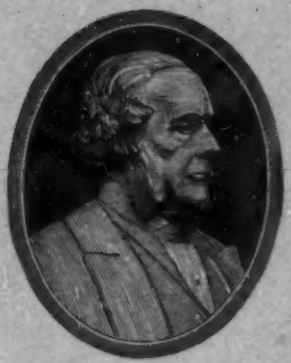
VOL. XLVIII ISSUED IN ALTERNATE MONTHS No. 211

The British Journal of Surgery



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BRISTOL: JOHN WRIGHT & SONS LTD.

WHOLESALE DISTRIBUTORS: WM. DAWSON & SONS LTD
10-12 MACKLIN STREET LONDON W.C.2

UNITED STATES OF AMERICA: THE WILLIAMS & WILKINS COMPANY, BALTIMORE, Sole Agents.

Entered as second class matter at the Post Office at BALTIMORE under Act of March 3, 1879.

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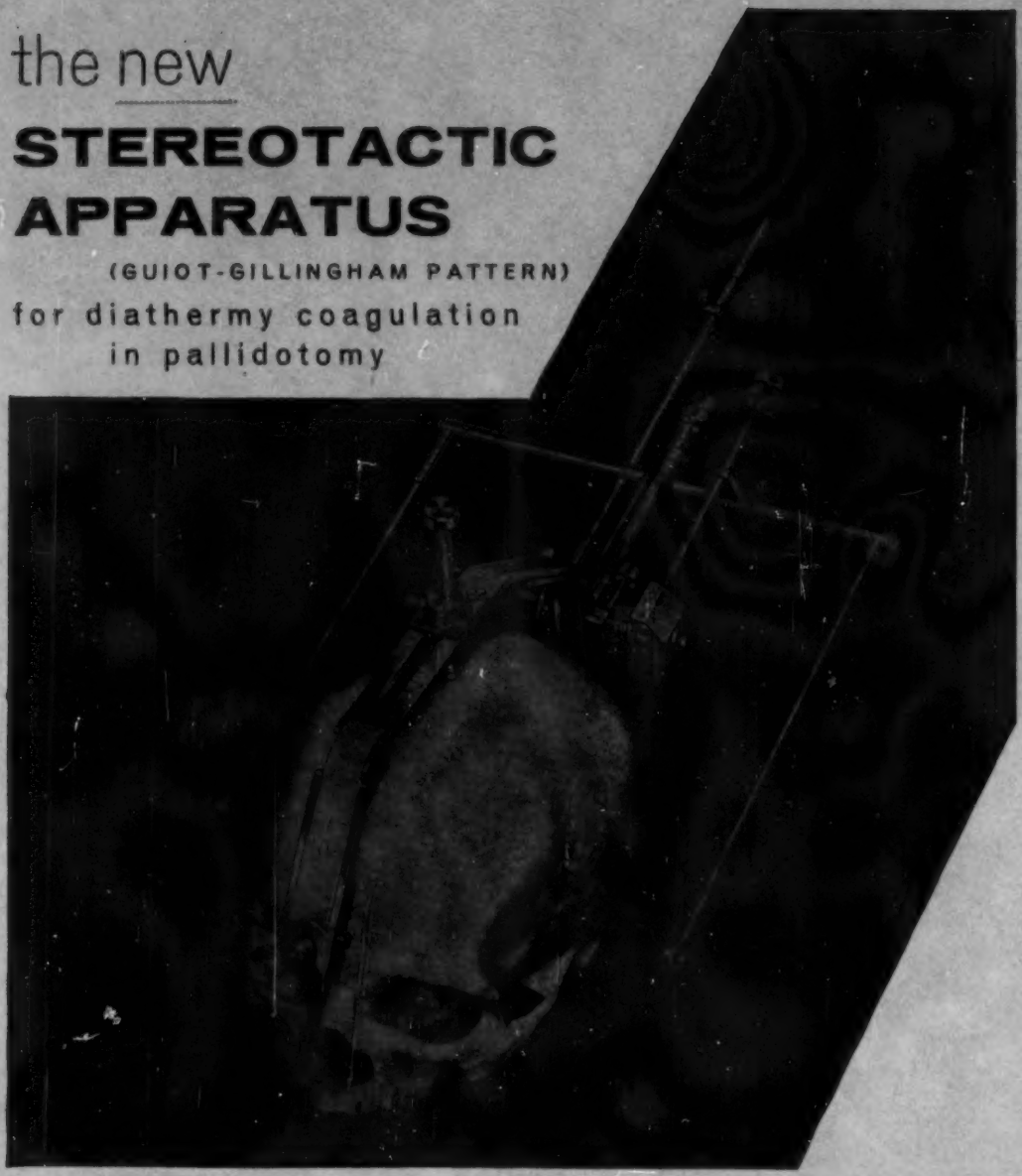
(GUIOT-GILLINGHAM PATTERN)

for diathermy coagulation in pallidotomy



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Reference: *Brit. med. J.* (1960), 2, 1395

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FRENCH'S
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EDITED BY

ARTHUR H. DOUTHWAITE, M.D., F.R.C.P.

Senior Physician, Guy's Hospital; Honorary Physician, Westminster Hospital and All Saints' Hospital for Genito-urinary Diseases

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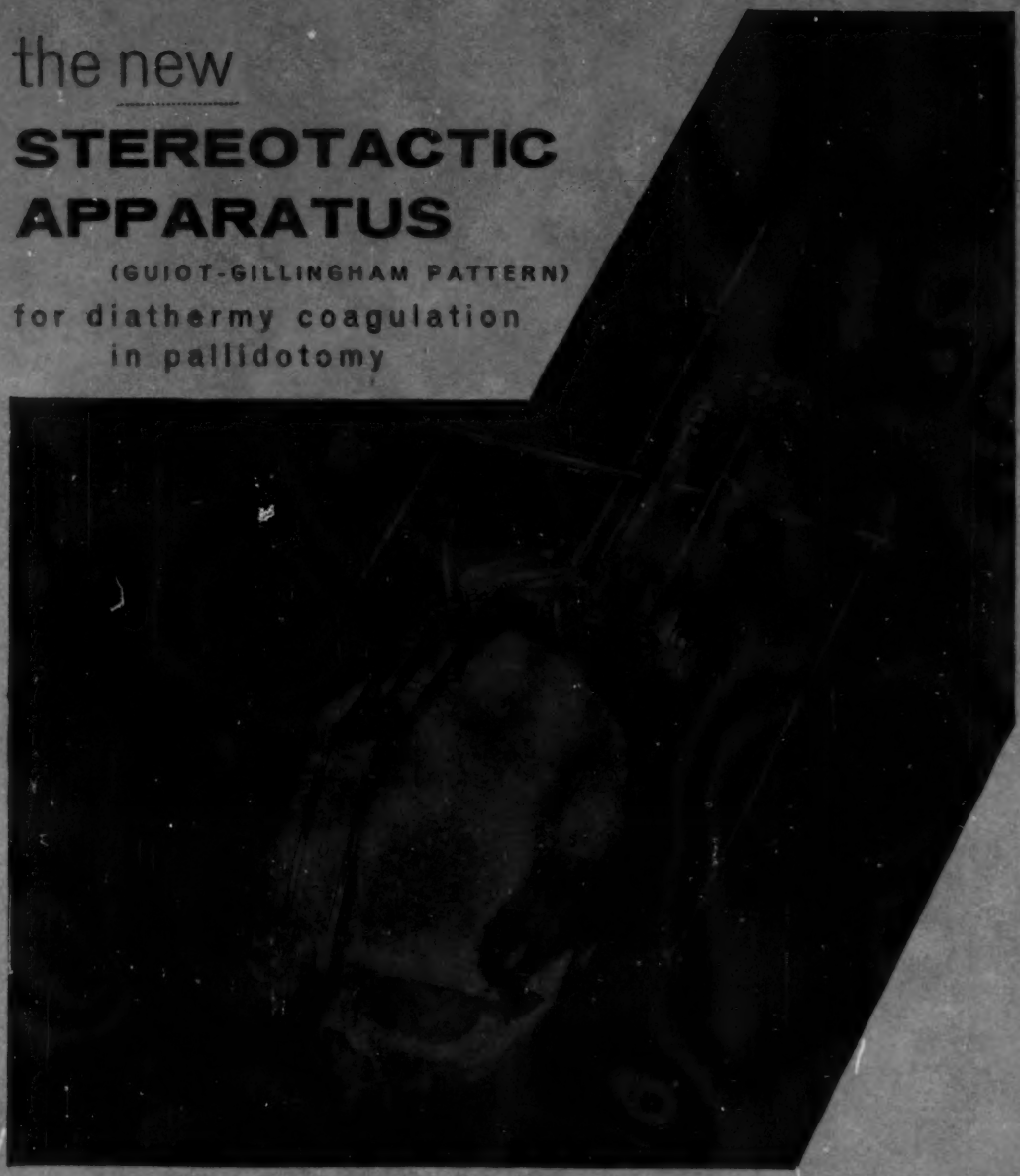

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SPECIMEN PAGE

œsophagus, or larynx, with *endothelioma* of the antrum, or with a sloughing *fibrosarcoma* of the nasopharynx. In children the possibility of some *foreign body* having become impacted in the throat, nose, or nasopharynx should not be forgotten.

Only when all such local conditions have been excluded, and when there is no acute illness or lesion of the lungs, can one attribute foulness of the breath to hepatic disease or dysfunction, to *constipation* or to *dyspepsia*. It is sometimes difficult to find out why the patient's breath is not sweet, and indeed there are some persons in whom all the functions of the body seem to be normal, and the mouth clean, and yet the breath is foul. If there are symptoms of gastro-intestinal disorder, especially flatulence or constipation, one is inclined to attribute the condition of the breath to the stomach or the bowels; but when there are no such symptoms it is more likely that the trouble is due to some local condition not discovered on inspection, particularly putrefaction of food particles impacted between the teeth even in persons who use both tooth-brush and mouth-wash regularly. X-ray examination of the teeth may be required before one can exclude periodontal or apical infections (*Figs.* 65–67, p. 55), particularly in association with old crowns which may superficially appear clean and sweet. *Adolphe Abrahams.*

BRUIT, INTRACRANIAL.—A systolic bruit may be heard over the skull in the presence of congenital arteriovenous angiomata of the brain (*Fig.* 136), but the absence of a murmur does not exclude the presence of such a lesion. A bruit commonly accompanies the pulsating proptosis of a carotico-cavernous fistula, usually the result of a head injury

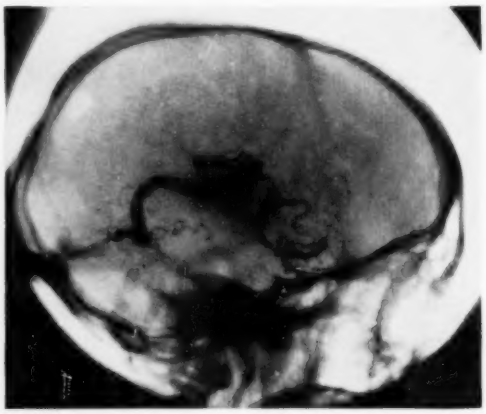

Fig. 136.—Common carotid angiogram showing angioma with feeding arteries and a large venous channel draining into the lateral sinus. (*From 'Clinical Neurology', by courtesy of Cassell & Co.*)

or of rupture of an intracavernous berry aneurysm. Berry aneurysms in the posterior fossa occasionally cause a bruit, a finding almost unknown in aneurysms above the tentorium.

Advanced Paget's disease of the skull, and arterial hypertension in young children, are rare causes of an intracranial bruit. Stenosis or kinking of the carotid artery in the neck can cause a harsh systolic murmur which may be conducted upwards into the occipital region; the systolic bruit of aortic stenosis can be conducted into the neck, but it is maximal over the aortic area, unlike the bruit which arises in the carotid artery itself.

F. A. Elliott.

BULLÆ.—A bulla or blister (*Fig.* 137) differs from a vesicle only in its size which is from half an inch in diameter to that of a tangerine orange. Many skin diseases may from time to time develop bullæ, but there are certain disorders of which they are characteristic.

Bullæ confined to a particular area occur in *burns and scalds*, after the application of certain *chemicals* to the skin, and sometimes in *frost-bite*. After contact with poison ivy (*Rhus toxicodendron*) the reaction may be so severe as to cause blistering. Friction due to ill-fitting footwear may cause blistering of the feet and the dermatitis caused by rubber

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even loss of the eye can occur from the exposure of the cornea. Careful watch is kept for any sign of corneal abrasion or infection; a pad needs expert application if closure of the lids is difficult. Tarsorrhaphy is not infrequently necessary, and orbital decompression (transfrontal or temporal) has often to be performed.

Isolated paralyses of individual ocular muscles or groups of muscles are nearly always nuclear in origin; basal growths rarely cause ocular paralyses of any extent on one side only, the affection sooner or later becoming bilateral.

In some rare cases of convergent or divergent squint with absence of binocular vision and good vision in each eye, there may be the power of alternate fixation with more or less evident diplopia. As a rule, however, the individual has the power of suppressing the image of the squinting eye, obtaining monocular vision.

Diplopia is a common symptom in the rare disease *botulism*, produced by the ingestion of the *Bacillus botulinis* (*Clostridium botulinum*). The diplopia may be masked by ptosis, and is usually accompanied by mydriasis, dysphagia, dysphonia, vomiting, cramps in the limbs, and, especially in fatal cases, coma. The diagnosis generally depends on a history of one or more persons having partaken of a meal of some canned food and developing, at intervals varying from six to thirty-six hours, a combination of the symptoms just described. The disease generally occurs, therefore, in small epidemics, and the diagnosis may be suspected before it is possible to confirm it by cultivating the bacillus from the remnants of food. Should any of the infected food have been thrown out into the poultry yard, the rapid mortality amongst the fowls may afford another clue to the nature of the malady.

Frank W. Law.

DIPSOMANIA.—The essential feature of dipsomania is a recurrent compulsion to drink alcohol to excess. The attacks are separated by intervals of weeks or months during which the patient may remain sober and well-behaved; he then experiences an irresistible urge to take liquor, usually the stronger kind and in large amounts. The bout lasts for several days, seldom longer, and in its course the drinker may appear silent and morose, or noisy and excited, or rude and aggressive, or muddled and silly. He may drink himself into a coma, recover and begin again. After the bout he generally suffers shame and remorse, and may try to make amends for any harm he has done.

Dipsomania can be a symptom of several mental disorders, and also an illness in its own right. During phases of elation and excitement in *mania*, and its lesser form, *hypomania*, a patient may take to the bottle, seeking perhaps to intensify his exuberance still further, or to quell anxiety. In one of his black moods the *depressive* may drink heavily, to drown his depression. Many victims of dipsomania belong to the category of *psychopaths*, and are irresponsible and immature in outlook. A *schizophrenic* illness may show itself first by spells of drinking; paranoid or other delusions, hallucinations, or signs of insanity, appearing during the spell, may give the clue to diagnosis. In some people, *brain injury* predisposes to periodic drinking.

Apart from these disorders, the recurrent craving for alcohol may be taken as a sign of the need to escape from some intolerable inward tension, notably the pressure of irrational guilt-feelings—alcohol is an excellent though temporary solvent of guilt. Continued over-consumption, however, even at intervals, tends to produce a deterioration of personality. In the periodic drinker there is commonly a striking difference between his behaviour in the sober intervals and his behaviour while drugged with alcohol; the difference may be such as to suggest a dual personality. The nature of the underlying conflicts engendering tension will be shown with more or less clarity by impulses and feelings expressed in the alcoholic state.

Desmond O'Neill.

DISCHARGE, NASAL.—A discharge from the nose may be unilateral or bilatera and consist of clear fluid almost like water, of mucus, mucopus, pus, food regurgitated through the nose, or blood. For the differential diagnosis of the causes of hæmorrhage from the nose, *see* EPISTAXIS, p. 303; of FOOD REGURGITATION, *see* p. 762.

Mucous and **Mucopurulent Discharges** differ from each other chiefly in degree, for that which may begin as mucous may later become mucopurulent as is seen during the course of a common cold. A watery discharge is sometimes spoken of as coryza, though for this to be typical there should at the same time be watering of the eyes; it is generally rapid in onset, and the diagnosis of its cause is, as a rule, not difficult. It may be due to the following different conditions:—

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OTORRHŒA.—Discharge from the ear may derive from the meatus itself, or from the middle ear through a hole in the tympanic membrane, or from the cranial cavity through tears in the meatal wall or the membrane.

Discharge due to Causes within the Meatus.—*Wax* is always being secreted by the ceruminous glands, and if that secretion is more profuse than usual it appears as a yellowish discharge; it is occasionally mistaken for a purulent discharge, especially when the wax has an unpleasant odour.

Blood escapes from the meatus as a result of wounds of its wall from damage caused by the introduction of foreign bodies or instruments, e.g., needles, pencils; small wounds may be self-inflicted by malingerers or neurotics. Fracture of the middle fossa of the skull may damage the bony wall of the ear and lead to bleeding from the meatus or to the escape of cerebrospinal fluid. Malignant ulceration in the meatus or middle ear also causes bleeding.

Serous discharge is frequently seen in diffuse acute eczema of the meatus, so profuse as to run from the ear.

Pus due to causes in the meatus is generally the result of boils or chronic meatitis; in the latter there is often great difficulty in deciding on the origin of pus as the membrane

Fig. 512.—A, Acute suppurative otitis media. B, Chronic otitis media, due to persistent tubotympanic infection. C, Chronic otitis, due to cholesteatomatous disease of the attic and mastoid antrum. D–F: Differential diagnosis of an inflamed area seen at the medial end of the meatus. D, The 'bulging membrane' of acute otitis media. E, The inflamed medial wall of the tympanum seen through a very large perforation, the result of chronic otitis. F, A polypus obscuring all details of the membrane. (*Illustrations by Miss S. Treadgold.*)

is hidden by marked narrowing of the canal; absence of deafness is helpful as proving the middle ear to be normal; in the case of boils, examination reveals tender swellings from which more pus can be pressed.

In a small percentage of cases of acute mastoiditis the suppuration spreads forwards through the bone and causes swelling of the posterior wall in the deeper, bony part of the meatus; this swelling may point and eventually burst into the meatus. When this occurs a sinus results and the appearance resembles that of a boil; this latter is excluded by the comparative absence of tenderness, by its position (boils do not occur in the bony meatus), and by the fact that a probe can be passed into the sinus and found to enter the mastoid process, or to touch bare bone.

Discharge due to Middle-ear Causes.—This may be (1) sanguineous, (2) serous, or (3) purulent.

1. *Sanguineous Discharge.*—Rupture of the tympanic membrane occurs from concussion either by a loud noise or from a blow on the ear, as in boxing or in diving if the side of the head hits the water, or from penetration by foreign bodies or from aero-otitis; bleeding results and the tear in the membrane may be seen on direct examination.

2. *Serous Discharge.*—In cases of very acute otitis media the fluid that escapes on rupture or incision of the membrane is serosanguineous at first, becoming purulent in two or three days. In some cases, however, notably those due to influenza or to hæmolytic streptococci, the discharge may remain serosanguineous for several days.

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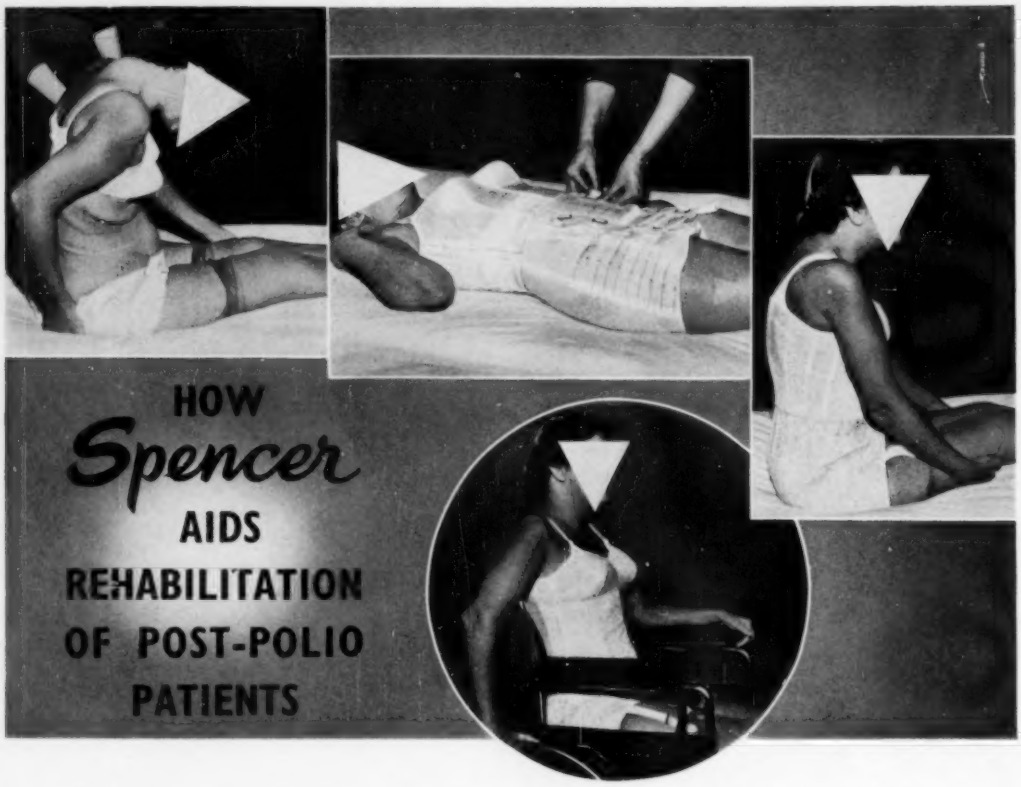

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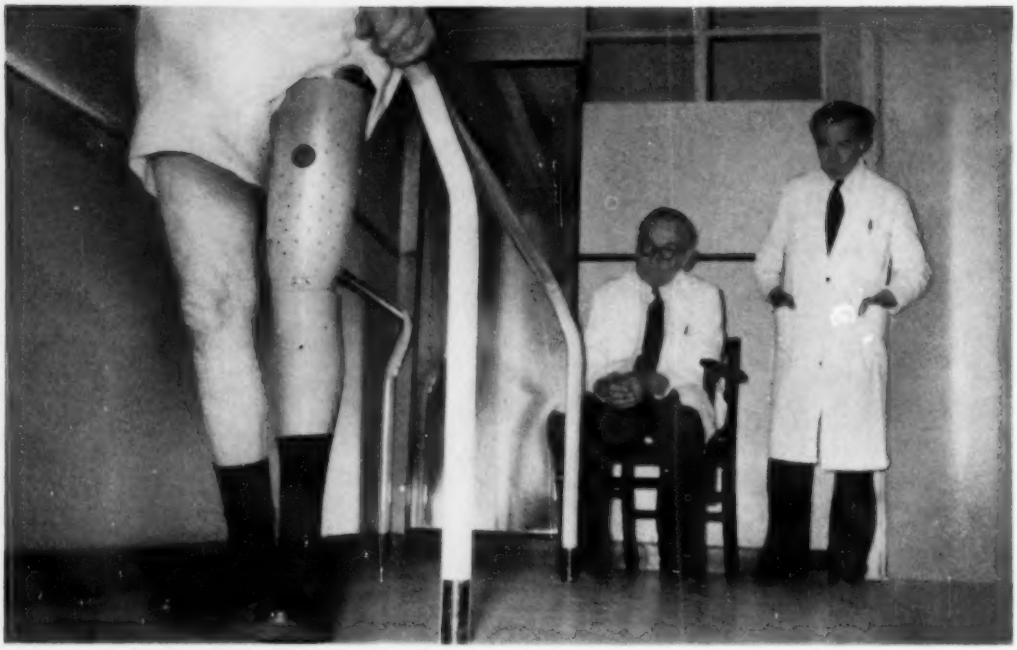

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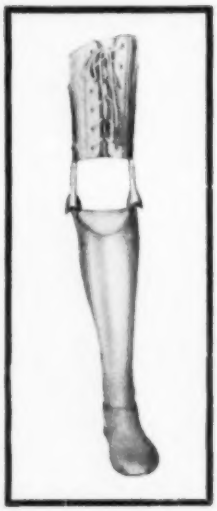

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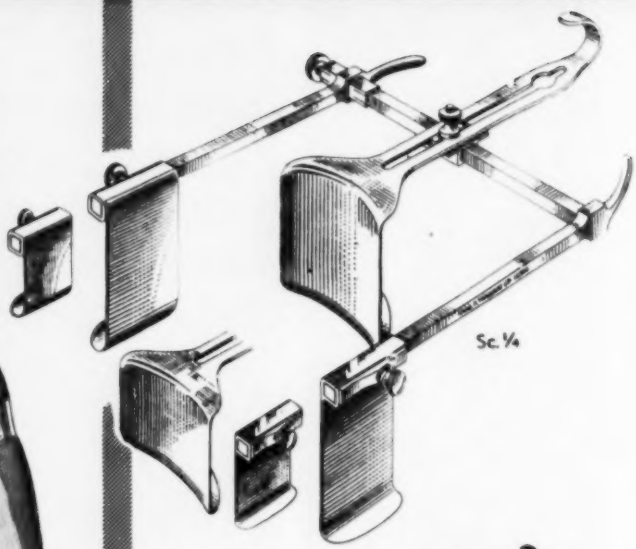

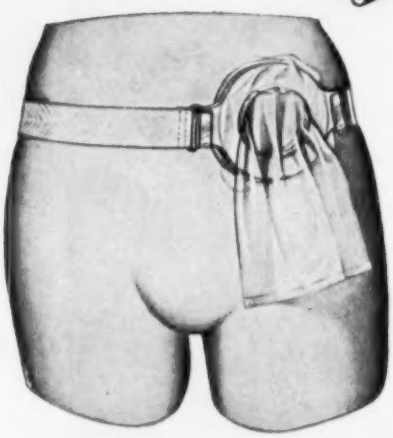

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Vide: "*The Lancet*", April 19th, 1958, pages 831-832.

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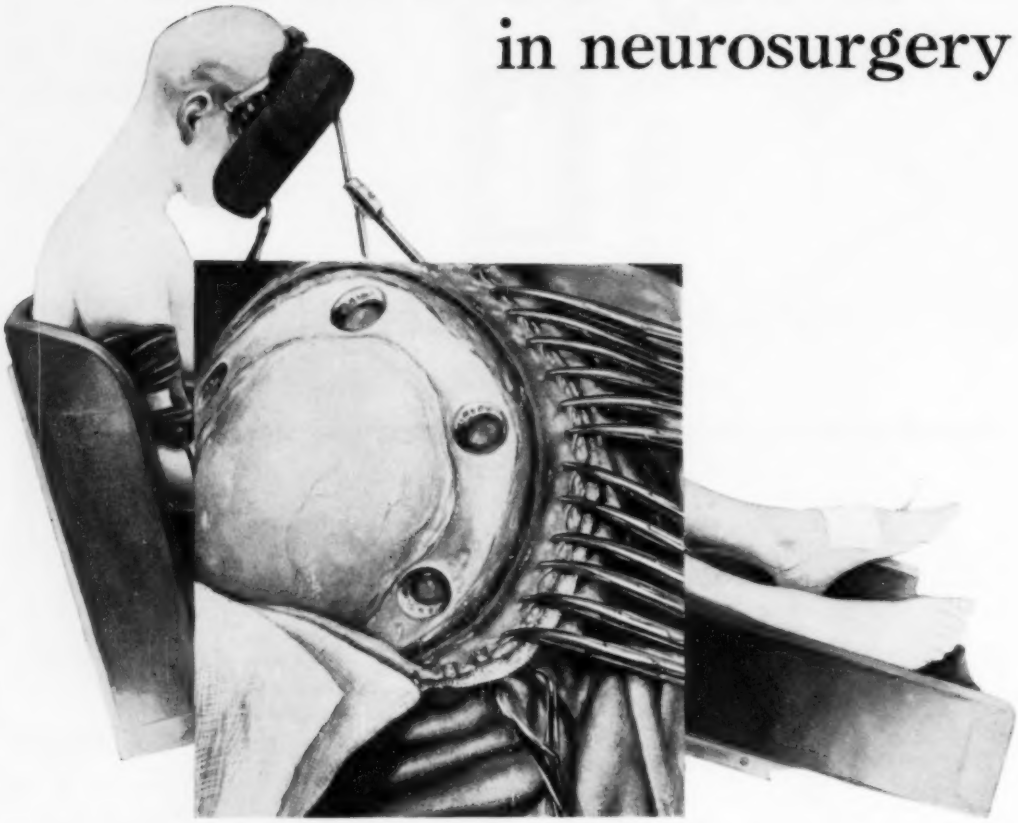

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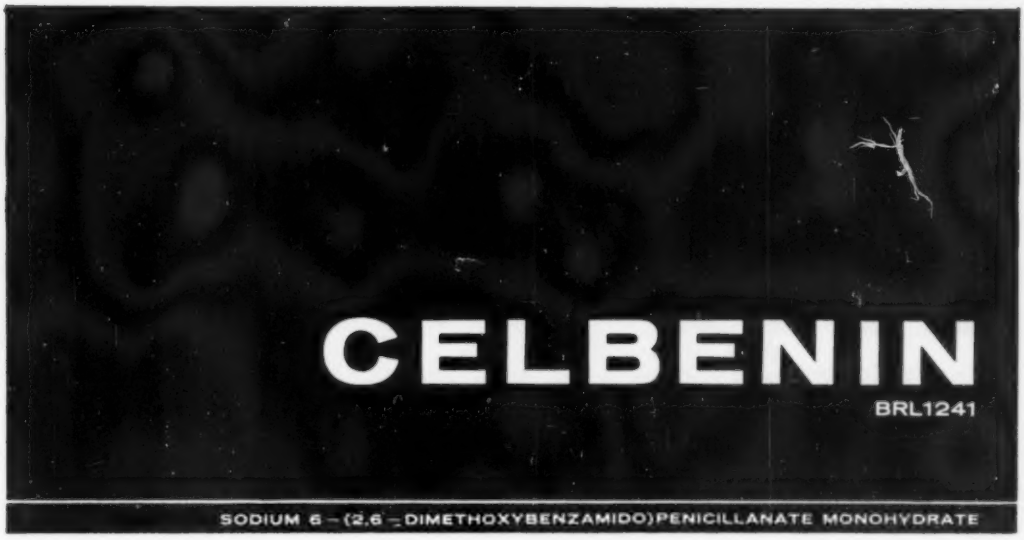

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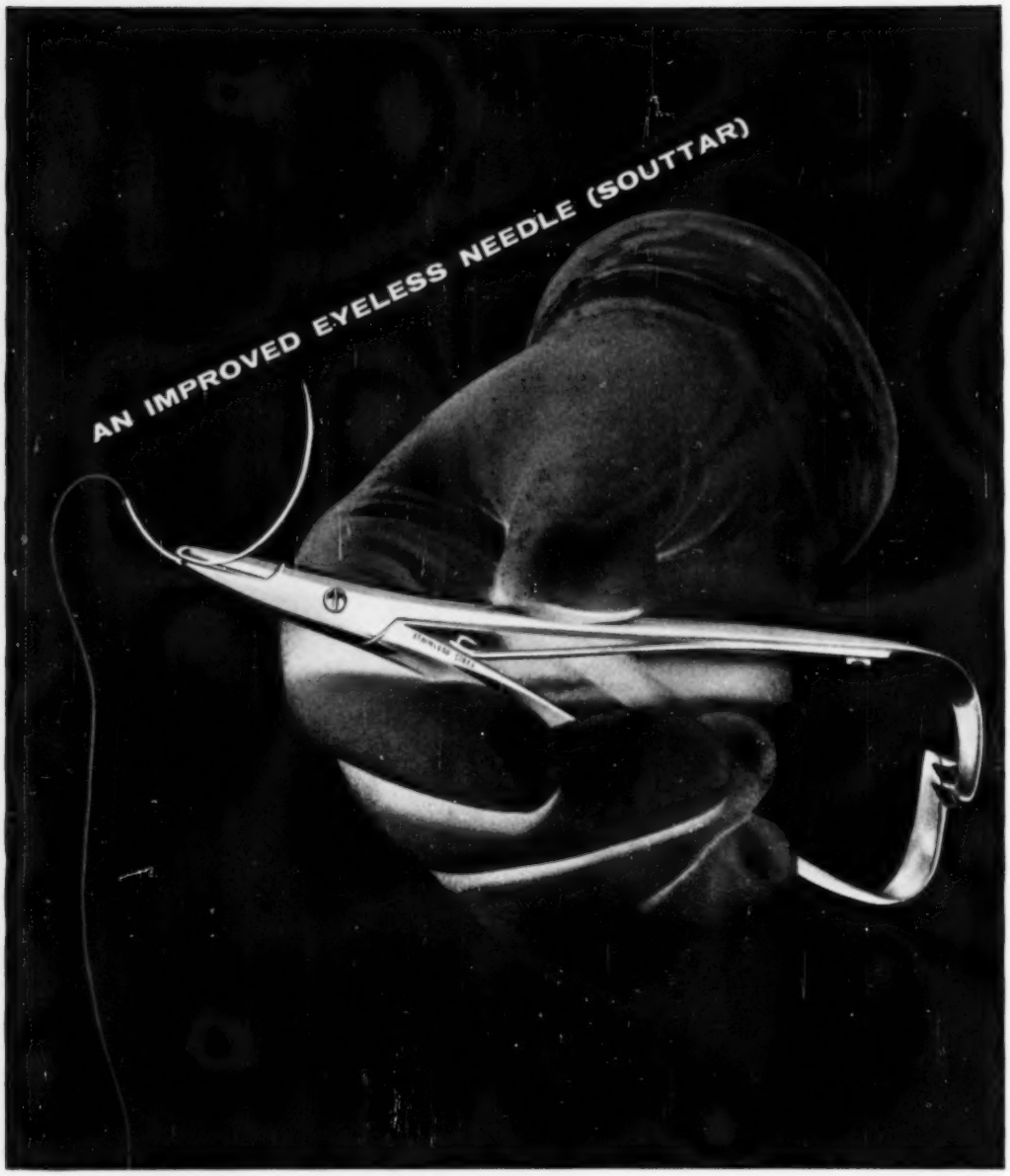

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THE
BRITISH JOURNAL OF SURGERY

VOL. XLVIII MARCH, 1961 No. 211

In Memoriam

Sir Ernest Finch, Kt., M.S., M.D., D.Sc. (Hon.), F.R.C.S., F.R.C.S.I.

(1884–1960)

THE death of Sir Ernest Frederick Finch at the age of 76 has left a void in the world of surgery which will be acutely felt by all fellow surgeons and a host of grateful patients. No man is indispensable, but Ernest Finch throughout his long professional life was so essentially a prominent figure in the pattern of surgery in this country that it is difficult to conceive that any one man could undertake the multitude of duties that he accepted.

He took a large part in the formation of the Sheffield Medical School, and lived to see it reach maturity with the full-time University Departments as we know them to-day. This is a far cry indeed from his early days in Sheffield, when although clinical study was permitted qualification had to be obtained elsewhere. He was also an indefatigable worker for the Royal College of Surgeons of England and never spared himself to further its progress.

His medical career commenced in 1901, and he graduated M.B., London, in 1906, later being given his M.B., Ch.B., Sheffield *ad eundem* after this University had been granted its charter. In 1909 he obtained the M.D., London. In 1911 he became a Fellow of the Royal College of Surgeons and took the degree of M.S., London, in 1913. He had already commenced his long association with the Royal Infirmary, Sheffield, where he became a house-surgeon in 1907, eventually being elected to the honorary staff in 1912. He served in the 1914–18 War, initially with a field ambulance and later with the 3rd Northern General Hospital. With the advent of peace he returned to his hospital and to private practice, becoming a lecturer in clinical surgery at the University. His hospital and private practice increased rapidly. As a penalty for fame he not infrequently had to make long and arduous journeys, maybe in severe weather, within a fifty-mile radius of Sheffield. To these he occasionally referred in later years.

In 1934 he was appointed to the part-time chair of surgery in this University. He gave enthusiastically and freely of his time for the benefit of the whole Medical School. His appointment as part-time professor terminated in 1944. Thereafter he still kept a very active interest in the Sheffield Medical School, although such good progress had been made, and was being made, that the steering hand of the helmsman was not so frequently needed.

He was elected to the Council of the Royal College in 1940 and became a vice-president in 1953, eventually retiring in rotation in 1956. Very many were the academic honours bestowed upon him—to mention a few: the Bradshaw lectureship, the Vicary lectureship, the Hunterian oration, and the Sheen lecture at Cardiff. He travelled far and wide on college duties. He was inspector of examinations on behalf of the General Medical Council. For ten years he was a member of the court of examiners and president of the Association of Surgeons of Great Britain and Ireland from 1939 to 1942. He was a member of the Moynihan Chirurgical Club for many years, acting as their secretary for twenty-one of these, and later becoming their president. In addition he was a member of the Executive Committee of the BRITISH JOURNAL OF SURGERY.

In the midst of all this he found time for attentive reading of medical publications, his chief interest being the history of medicine, and on this subject he held an honorary lectureship.

In 1951 he was honoured with a knighthood, a fitting and well-earned acknowledgement of his great work. In 1953 he was given the honorary degree of D.Sc., Sheffield, and in 1959 the honorary fellowship of the Irish college. Despite all these professional commitments he still had time to show an interest in Sheffield as a city, and in 1946 was elected a member of the Sheffield Town Trust.

Ernest Finch was a man of great charm of manner. Among his many gifts were those of equanimity and quiet humour, leadership and friendship, sympathy and kindness. Many a 'lame dog' he helped 'over the stile' with advice and encouragement, and many a practitioner and consultant looks back now with gratitude to Ernest Finch. In this he never let his right hand know what his left hand did; also if Ernest Finch promised to do anything one could be certain it would be attended to at the earliest possible moment. Nothing was too small, nothing too big, for his attention.

Early in his career he was sought after by students for his teaching ability. He was a big believer in emphasizing the importance of basic essentials. Old students frequently referred to Ernest Finch's frequent questions, "What are the characteristics of inflammation?" "What are the characteristics of a neoplasm?", and then later the application of these

fundamentals to the case under discussion. His manner was quiet and he rarely, if ever, raised his voice in class. Seldom, if ever, was he satirical at a student's expense, and if he was so the 'barb was blunted' by a friendly smile and often a comforting personal word afterwards while linking his arm with his 'victim'.

He was essentially a practical surgeon, putting the welfare of the patient foremost. Scientific curiosity as such was of necessity of secondary importance, though he was ever ready by investigation and observation to advance the progress of surgery. His quiet, sympathetic, kindly manner instilled confidence and made him beloved by patients of all classes.

His registrars and housemen revered him, and in 1949 as a practical expression of their respect and affection for him they contributed over £400 for the establishment of the Ernest Finch Library at the Royal Infirmary, Sheffield.

It was customary for many years, long after his retirement, for anyone faced with a difficult problem concerning, perhaps, surgical practice, hospital administration, or medical ethics, to go to Sir Ernest and seek his advice. His days seemed to be occupied with interviews and consultations over such matters. The advice given was shrewd and apposite, well considered, and given from a fund of knowledge and experience. He excelled at negotiations, often reconciling opposite points of view. He achieved this, not by *tour de force*, but by quiet reasoning and an ability to see and appreciate widely different outlooks and opinions.

During the last ten years he faced illness with almost incredible courage, and although he knew the end was inevitable he always showed gratitude for the years he was spared. During the last twelve months of his life few men, other than the people close to him, would have realized the suffering he was undergoing. Visitors would be met with a welcoming smile and discussion would be wide and varied. Within literally a few hours of his death he was discussing with his colleagues the future of the Medical School and his other great love, the Royal College of Surgeons. He knew that he was dying, and one of his last spoken sentences in response to a colleague's "Goodnight, and I will see you in the morning, Sir Ernest", was "I think you will see me, but I do not think I shall be able to see you". 'Of such stuff are great men made!'

In 1912 Sir Ernest married Miss Mary Ainsworth, who survives him with their son Michael.

SIR ERNEST FINCH

VENOUS THROMBOSIS AND PULMONARY EMBOLISM

A CLINICO-PATHOLOGICAL STUDY IN INJURED AND BURNED PATIENTS

By SIMON SEVITT

CONSULTANT PATHOLOGIST, BIRMINGHAM ACCIDENT HOSPITAL

AND NIALL GALLAGHER*

REGISTRAR-IN-PATHOLOGY, BIRMINGHAM ACCIDENT HOSPITAL

SURGEONS are not unfamiliar with the death from pulmonary embolism of patients with a fractured femur or other injuries, and embolism is recognized as an important cause of illness and death in many surgical and medical conditions and in obstetrics. The present study, which was carried out between 1952 and 1959, was stimulated by the common finding of fatal pulmonary embolism at necropsy often in patients in whom it had not been suspected. Venous dissection of the lower limbs of cases without embolism showed that thrombosis is very common, but prior clinical investigation showed that only about a third had had clinical effects (silent thrombosis). A very high incidence of thrombosis is associated with advancing age and a period of bed-rest longer than a few days, whilst the nature of the injury has little *direct* influence.

The patterns of thrombosis found indicate multiple primary sites of thrombosis, 4 in the thigh and pelvic veins and 2 in the calf veins. Thrombosis may begin independently at one or more and then extend to involve other parts of the deep venous tree. Thrombosis is generally bilateral; this includes patients with injury confined to one limb and patients with unilateral clinical thrombosis.

PRESENT STUDY

This report is based on three inter-related studies: (1) Venous thrombosis found at necropsy; (2) Pulmonary embolism clinically and at necropsy; and (3) A special investigation on cases with fractured hips in which a combined clinical and pathological study of venous thrombosis and pulmonary embolism was made.

Unselected necropsies were dissected for venous thrombi. Those without pulmonary embolism (125 cases) were separately analysed, whilst those found to have embolism were included in the embolism series. Venous dissection was also done on all cases with emboli. The 125 cases were not consecutive but their diagnoses represent the types of cases which come to necropsy in the Birmingham Accident Hospital (*Table I*). Their separation permitted an analysis of the patterns of thrombosis undisturbed by embolism and the frequencies of thrombosis at different times after injury and in different age groups. A combined analysis of the cases without and with embolism was not done because it is likely to exaggerate the frequencies of thrombosis and embolism; when embolism was diagnosed or suspected special efforts to obtain permission for necropsy were often made whilst many other deaths did not reach necropsy. The embolism group therefore contains clinically diagnosed (or suspected) and unsuspected cases. *Table I* also gives the diagnoses and numbers of cases with embolism related to the total number of necropsies.

The special series with fractured hips numbered 160 cases and were mostly the 'control series' of a clinical trial of prophylactic anticoagulant therapy (*see* Sevitt and Gallagher, 1959). Most of those who

Table I.—INCIDENCE OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM AT NECROPSY

(Note that the two series are not identical in that the venous thrombosis series does not include any cases with pulmonary embolism. The frequency of embolism is based on all the cases in which necropsy was performed during the period of the study, which includes the venous thrombosis series.)

Injury	Venous Thrombosis (Cases without Embolism)		Pulmonary Embolism	
	No. of Necropsies Specially Studied	No. and Percentage with Venous Thrombosis	No. of Necropsies	No. and Percentage with Pulmonary Embolism
Fractured neck of femur	47	39 (83)	114	52 (46)
Other fractures of femur	7	6 (86)	17	9 (53)
Fractured tibia	—	—	10	6 (60)
Fractured pelvis	2	2 (100)	40	11 (27)
Fractured spine	2	1 (50)	21	3 (14)
Head injury	19	10 (37)	135	6 (4·4)
Head and chest injury	8		47	1 (2·1)
Abdominal and or thoracic injury	5	2 (40)	72	4 (5·5)
Other injuries	2	1 (50)	12	3 (25)
All trauma cases	92	61 (66)	468	95 (20·3)
Burns	33	20 (60)	163	9 (5·5)
TOTALS	125	81 (65)	631	104 (16·5)

* Now Pathologist, Sir Patrick Dun's Hospital, Dublin, Ireland.

died came to necropsy and the post-mortem findings were correlated with the frequent clinical examination for thrombosis and embolism.

Necropsy Techniques.—The lower venous tree was examined for thrombi by opening with scissors the inferior vena cava at the diaphragm to the posterior tibial veins at the ankles. This exposed the vein contents and the thrombi in situ. The technique was usually simple because the thrombi were generally not adherent to the walls of the veins. First, the vena cava and the common, internal, and external iliac veins were opened. The inguinal ligament was then divided and the incision continued distally along Hunter's canal. The common and superficial femoral veins were opened along their entire length; the profunda femoral vein was split open and also the terminal parts of the great saphenous vein and as much as possible of the medial and lateral circumflex veins and other large intramuscular veins. The body was then turned face downwards; a deep oblique incision was made behind each knee joining the distal end of the incision in the thigh to the upper end of the mid-calf; the adductor ring was cut through and the popliteal vein was exposed. A deep midline incision down the back of the leg to the ankle, splitting the gastrocnemius and the soleal muscles longitudinally, exposed the posterior tibial veins; the popliteal and the posterior tibial veins were then opened as far as the ankle. The veins within the soleal and gastrocnemius muscles and especially the soleal plexus were examined for thrombi usually by multiple deep transverse cuts in the muscles.

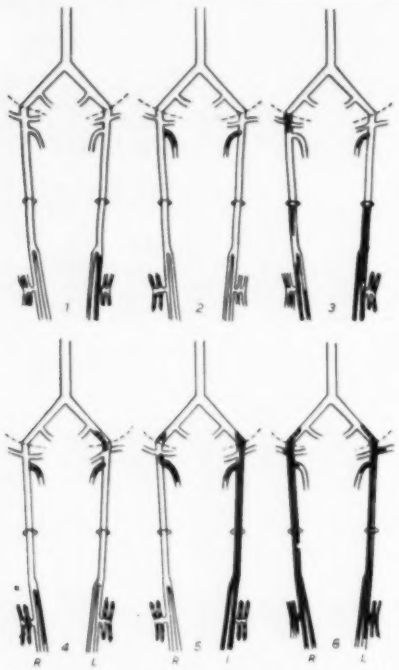

FIG. 543.—Diagrams of deep vein thrombosis found at necropsy in the lower limbs of 6 injured patients. The cases are selected to show the independence of thrombosis in the 6 main primary sites (*see Fig.* 544) and the variety of patterns of thrombosis which occurs (*see* text).

The position, extent, and nature of the various thrombi found were recorded on diagrammatical charts of the venous system (*Fig.* 543).

The pulmonary arteries were laid open with scissors and examined for emboli from the bifurcation to the peripheral branches of lobar arteries.

DEEP VEIN THROMBOSIS

Frequency at Necropsy.—Thrombosis was found in 81 of the 125 cases without embolism (65 per cent). The incidence would have been even higher if cases with pulmonary embolism had not been excluded because they always had thrombosis. Estimates of venous thrombosis among medical and surgical necropsies range from 44 per cent to 60 per cent (Neumann, 1938; Hunter, Krygier, Kennedy, and Sneeden, 1945; Gibbs, 1957). The frequency in any series of necropsies depends mainly on the ages and survival periods (bed-rest) of the patients (*see later*) and therefore depends on the proportions of different cases in the series.

Table II.—FREQUENCY OF THROMBOSIS IN ILIOFEMORAL, POPLITEAL, AND CALF VEINS AT NECROPSY AMONG 81 CASES WITH THROMBOSIS BUT NO EMBOLISM

LIMBS OR PATIENTS (Total No.)	ILIO-FEMORAL THROMBOSIS	POPLITEAL THROMBOSIS	CALF-VEIN THROMBOSIS
	per cent	per cent	per cent
Limbs: Right, 81	46	22	62
Left, 81	53	25	66
Both, 162	49	23	64
Patients, 81	70	37	74

Leg, Thigh, and Pelvic-vein Thrombosis at Necropsy.—Among the 81 cases with thrombosis, thrombi were most common in veins of the calf (74 per cent of the cases and 64 per cent of the limbs), was frequent in the pelvic and/or thigh veins (70 per cent of cases and 49 per cent of limbs), and was less frequent in the popliteal veins (37 per cent of cases and 23 per cent of limbs) (*Table II*).

Tables II–IV show that thrombosis was more common in the left than the right lower limb (89 per cent compared with 74 per cent of the cases), mainly because of more frequent thrombosis in the left iliac and femoral veins. Thrombosis was more frequent in the intramuscular veins of the calf, usually the soleal plexus, and was found in 48 per cent of the 162 limbs and in 67 per cent of the 81 cases (*Table III*). Next were the posterior tibial veins, with 39 per cent of the limbs and 54 per cent of patients affected. Common femoral thrombosis was found in 27 per cent of limbs and 48 per cent of cases, whilst thrombi were as frequent in the profunda femoral vein (28 per cent of limbs, 43 per cent of patients). Popliteal vein thrombosis, with 20 per cent of limbs and 33 per cent of cases, and superficial femoral vein thrombi, with 20 per cent of limbs and 31 per cent of cases, were next in frequency. Thrombi in the external iliac vein were found in 17 per cent of limbs and 26 per cent of patients; thrombosis of the common iliac veins was less frequent (8·6 per cent of limbs, 11 per cent of

cases). An infrequent site was the internal iliac vein, with thrombi in 5·5 per cent of limbs and 8·6 per cent of patients. Thrombosis had extended into the inferior vena cava in 5 per cent of patients.

Thrombi in the *same* individual veins of both limbs were relatively uncommon except for the veins of the calf. Thrombi in the intramuscular veins of both calves were present in 29 per cent of cases and in without thrombi in the veins of the calf (*Cases* 1 and 2). Thigh and leg vein thrombosis may be separate (*Cases* 2–5) or as a continuous thrombus (*Cases* 5, 6). Thrombosis in the external iliac vein may or may not be associated with thrombosis in the common femoral vein (*Cases* 4–6). Thrombosis in the profunda femoral vein was often isolated from thrombi elsewhere (*Cases* 2–4) (*Figs.* 545, 548), although sometimes it extended

Table III.—Thrombosis in Various Deep Veins in 81 Necropsies without Pulmonary Embolism
(Numerals refer to number of limbs or patients.)

	No.	Pelvic Veins			Thigh Veins				Calf Veins		Inferior Vena Cava
		Common Iliac	External Iliac	Internal Iliac	Common Femoral	Superficial Femoral	Profunda Femoral	Popliteal	Posterior Tibials	Soleal and Gastrocnemius Veins	
Right lower limbs	81	7	11	4	19	13	16	14	28	36	4
Left lower limbs	81	7	17	5	25	20	29	19	35	42	
Right and left limbs	162	14	28	9	44	33	45	33	63	78	
Patients	81	9	21	7	39	25	35	27	44	54	
Bilateral thrombosis	81	5	7	2	5	8	10	6	19	24	

both posterior tibials in 23 per cent. Bilateral thrombosis of individual pelvic and thigh veins ranged from 2·5 per cent involving both internal iliacs to 12 per cent involving both profunda femorals.

Patterns and Distribution of Thrombosis.—The combinations of veins and vein groups (calf veins, iliofemoral veins, and popliteal vein, alone and in various combinations) affected by thrombi varied considerably and were often different even in the two limbs (*Table IV*). Thrombi only in calf veins were found in 28 per cent of the 162 limbs, only in iliofemoral veins in 17 per cent, whilst thrombosis of the popliteal vein never occurred by itself. The most frequent combination was the calf veins, popliteal and iliofemoral veins (18 per cent of limbs), whilst thrombi in the combinations of calf veins and iliofemoral veins involved 13 per cent of limbs. The combinations of popliteal vein thrombosis with thrombi only in calf veins (4 per cent) and with thrombi only in iliofemoral veins (1 per cent) were infrequent.

These findings throw light on the sites of origin of thrombi. There are two main but conflicting views on this: The concept that thrombi originate in the calf veins and extend into the thigh is based largely on the fact that symptoms of venous thrombosis, particularly limb swelling and pain, commence in the calf. The other view that thrombi arise in the iliofemoral vein (Aschoff, 1924) is based on vein dissections at necropsy on patients with clinical thrombosis or embolism. These differences have been resolved in the present investigation and in general support the findings of Frykholm (1940) and Gibbs (1957). *Fig.* 543 illustrates the patterns of thrombosis found in the 12 limbs of 6 cases without embolism. These are *selected* to show the independence of thrombosis in various deep veins (*Cases* 1–4) and continuous thrombosis in thigh and leg veins (*Cases* 5 and 6). Thrombosis in iliac and femoral veins may occur independently or separately (*Fig.* 545) or as a continuous thrombus (*Figs.* 546, 547); and either with or upwards into the common femoral vein (*Case* 5) or even above the inguinal ligament. A thrombus in the popliteal vein usually communicated with thrombosis in the posterior tibial veins (*Case* 3), but occasionally it was separate. Thrombosis of the veins in the calf muscles and of the posterior tibial veins were

Table IV.—Thrombosis in Calf Veins, Popliteal Veins, and Iliofemoral Veins (and in Various Combinations) of 162 Limbs of 81 Cases with Thrombosis but no Embolism at Necropsy

Veins with Thrombi	Right Limbs	Left Limbs	Right + Left Limbs
	per cent	per cent	per cent
Calf veins only	25	32	28
Iliofemoral veins only	11	23	17
Popliteal vein only	0	0	0
Calf veins + iliofemoral veins	17	9	13
Calf veins and popliteal veins	4	4	4
Iliofemoral veins and popliteal veins	1	1	1
Calf veins, iliofemoral and popliteal veins	16	20	18
Total with thrombosis	74	89	81

commonly present in the same limbs, but one could occur without the other. It is of interest that thrombosis in the superficial femoral vein never occurred in isolation. Thrombosis in this vein was generally continuous along its whole length, extending from the common femoral to the popliteal vein (*Cases* 5, 6) (*Figs.* 546, 547). This indicated that its thrombosis was retrograde and probably followed proximal venous blockage. Only occasionally was a thrombus in the superficial femoral vein not continuous with one in the common femoral; then it was continuous with a thrombus in the popliteal vein and terminated at various levels in the superficial femoral vein as if it had propagated centrally from the popliteal vein.

Primary Sites of Thrombosis.—The variety of patterns of thrombosis indicates that thrombosis can begin at one or more of several independent sites. Six main primary sites are recognized (*Fig.* 544), viz.: (1) The iliac vein, generally the external iliac vein just above the inguinal ligament; (2) The common femoral vein, including the mouths of the medial and lateral circumflex veins; (3) The termination of the deep femoral vein, usually at a valve cusp guarding the ostium; (4) The popliteal vein near the adductor ring; (5) The posterior tibial veins; and (6) The intramuscular veins of the calf, particularly the soleal veins. Thrombosis extends from the primary thrombi

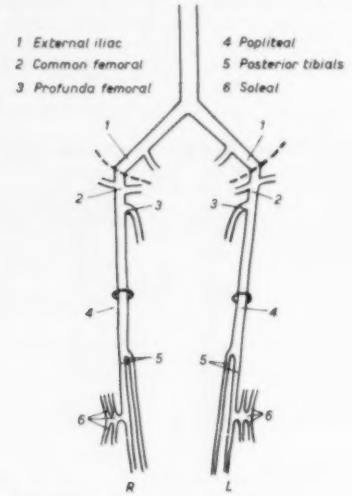

FIG. 544.—Diagrammatic outline of the lower venous tree showing the 6 main sites at which deep vein thrombosis begins. These primary sites are independent of each other, although thrombosis is frequent in two or more of them.

FIG. 546.—Continuous long thrombus extending from the external iliac vein to the popliteal vein and communicating with a long thrombus in the deep femoral vein.

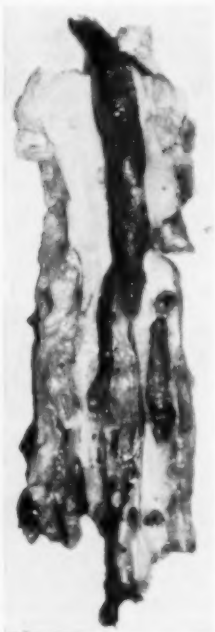

FIG. 545

FIG. 547

FIG. 545.—Thrombus in the common femoral vein (top half of figure) propagating upwards from the junction of the superficial and deep femoral veins. Note also the smaller independent thrombus in the deep femoral vein (bottom half of figure, right) taking origin from a valve cusp.

FIG. 547.—Continuous iliofemoral thrombosis of the left limb with none in the right limb. The patient died from a large pulmonary embolus which probably originated from the right iliofemoral vein.

by central propagation or by retrograde extension or through both processes.

The concept of multiple sites of thrombosis is supported by evidence derived from the prophylactic trial of phenindione against thrombosis (Sevitt and Gallagher, 1959). When prophylaxis was delayed for a few days after injury so that thrombi may have already begun to form, but could not then extend, small thrombi may be found at necropsy especially in the soleal vein, the posterior tibial vein, and the termination of the profunda femoral (*Fig.* 549).

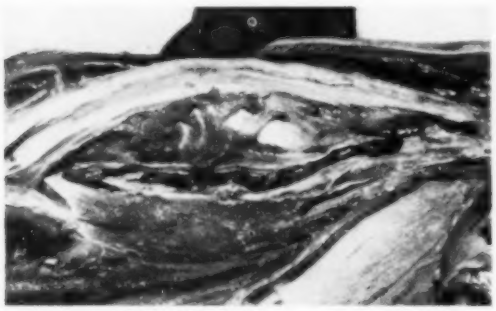

FIG. 548.—Long thrombus in the deep femoral vein and no thrombosis in the common or superficial femoral veins.

FIG. 549.—Small primary thrombus in a valve cusp at the mouth of the deep femoral vein.

Relation of Venous Thrombosis at Necropsy to Age and Survival Period (Bed-rest).—Thrombosis becomes more frequent at necropsy with increasing duration of survival period after injury and advancing age (*Tables V–VII*). *Table V*, in which survival period may be taken as equivalent to the duration of bed-rest, shows that the frequency of thrombosis rises rapidly during the first week after injury from 19 per cent of 26 cases dying within 4 days to 47 per cent of 19 cases dying between 4 and 7 days. After this it rises further to between 75 per cent and 90 per cent in those dying at various times during the next few weeks. The rising incidence affects the veins of the thigh and calf and the popliteal veins. Prolonged bed-rest (more than 28 days) is associated with a particularly high rate of thigh vein thrombosis (73 per cent of 30 cases), and this is important in view of the large risk of serious embolism from these wide-calibre and often long thrombi. With regard to age (*Table VI*), most patients (75 per cent) over 60 years of age die with thrombosis and more than half of those over 45 years, but even in young people thrombi are not infrequent: 31 per cent of those under 15 years had thrombosis. Advancing age is associated with a rising frequency of thrombosis in the veins of both the thigh and calf. Taking age and survival period together (*Table VII*) it is clear that the risk of thrombosis is particularly large in middle-aged and elderly patients who survive longer than 3 days and is much less in those under 45 years of age dying within a week of injury. This broad separation is useful in the primary selection of groups of patients for routine prophylaxis with anticoagulant drugs (*see* Sevitt and Gallagher, 1959). Even so, the risk of thrombosis is not negligible within 7 days or even within 3 days of bed-rest, particularly in the elderly.

Evidence was obtained that thrombogenesis may continue for weeks. Although the ages of thrombi

Table V.—SURVIVAL PERIOD AND FREQUENCY OF VENOUS THROMBOSIS

(Deep vein thrombosis at necropsy among 125 cases without pulmonary embolism. No. of cases related to period of survival after injury and vein groups.)

Survival Period (days)	Total Cases	Cases with Thrombosis (Unilateral or Bilateral)			Cases with Thrombosis in any Vein
		Thigh Veins	Popliteal Veins	Calf Veins	
<4	26	2	0	5	5 (19 per cent)
4–7	19	6	5	7	9 (47 per cent)
8–14	25	14	8	19	22 (88 per cent)
15–21	13	7	6	8	10 (77 per cent)
22–28	12	5	3	6	8 (75 per cent)
>28	30	22	8	15	27 (90 per cent)

Table VI.—AGE AND FREQUENCY OF VENOUS THROMBOSIS

(Deep vein thrombosis at necropsy among 125 cases without pulmonary embolism. Frequency related to age and vein groups.)

Age-group (years)	Total Cases	Cases with Thrombosis (Unilateral or Bilateral)			Cases with Thrombosis in any Vein
		Ilio-femoral Veins	Popliteal Vein	Calf Vein	
<15	13	3	2	4	4 (31 per cent)
16–30	14	5	3	6	9 (64 per cent)
31–45	7	1	1	2	3 (43 per cent
46–60	16	7	1	5	9 (56 per cent)
61–75	24	11	5	14	18 (75 per cent)
>75	51	29	18	29	38 (75 per cent)

are notoriously difficult to estimate, those discoloured by hæmosiderin or adherent to a vein wall are obviously older than those which are not discoloured and non-adherent. Many patients dying weeks or months after injury had both kinds and their distribution indicated that thrombi were laid down on two, three, or more occasions over a period of weeks.

Table VII.—Incidence of Deep Vein Thrombosis at Necropsy related to Age and Survival Period

(Thrombosis in any site in one or other lower limb among 125 cases *without* pulmonary embolism. Numerals are the number of cases with thrombosis/number of cases in the group.)

Age Group (years)	Survival Period (days)								Totals
	0–3	4–7	8–10	11–14	15–21	22–28	29–35	>35	
<15	0/2	0/4			0/2	4/5			4/13
16–30	1/1	0/3	3/3	2/2		0/1	2/2	1/2	9/14
31–45	0/3	0/1		1/1	2/2				3/7
46–60	3/8	2/4					2/2	2/2	9/16
61–75	1/5	2/2	5/5	3/4	0/1	2/2		5/5	18/24
>75	0/7	4/4	6/7	2/3	9/9	4/5	2/2	11/14	38/51
All ages	5/26	8/18	14/15	8/10	11/14	10/13	6/6	19/23	81/125

Table VIII.—Frequency of Unilateral and Bilateral Venous Thrombosis at Necropsy

	Total No.	Unilateral Thrombosis	Bilateral Thrombosis	Unilateral or Bilateral Thrombosis
		per cent	per cent	per cent
Cases without pulmonary embolism	125	23	42	65
Cases with pulmonary embolism	104	23	77	100

This means that thrombogenesis is not confined to the first week or two after injury.

Unilateral and Bilateral Thrombosis at Necropsy.—The frequency of unilateral and bilateral thrombosis is shown in *Table VIII*. Among those without pulmonary embolism, bilateral thrombosis was almost twice as common (42 per cent of cases) as unilateral thrombosis (23 per cent), whilst in those with pulmonary embolism bilateral thrombosis was even more frequent (77 per cent) than unilateral thrombosis (23 per cent). Bilateral thrombosis is then largely the rule and this is so even when clinical swelling or pain is restricted to one limb.

Nature of the Injury and Venous Thrombosis.—The frequency of thrombosis is only indirectly related to the injury. The main influences are age and survival period (bed-rest), but these are often related to the nature of the injury, whilst survival period is often influenced by therapy. Compare the three groups of patients dying after head (or head and chest) injury, burns, and fractured neck of femur (*Table IX*); the incidence of thrombosis at necropsy was 37 per cent, 60 per cent, and 83 per cent respectively. The lowest figure is associated with a large proportion of cases with a short survival period, few of whom had thrombi; the very high rate is related to relatively long survival periods combined with advanced age, whilst the intermediate rate of those with burns is associated with a relatively even mixture of children, adults, and elderly patients most of whom survived longer than a week. Survival and prolongation of life may also be related to therapy, which would then indirectly influence the frequency of thrombosis. For example, the relatively high frequency of thrombosis in burned patients now reported is likely to be an indirect result of modern transfusion therapy; many of those who would have previously died during the shock-phase generally without venous thrombosis now

Table IX.—Frequency of Venous Thrombosis at Necropsy related to (A) Survival Period and (B) Age, in Patients dying after: (1) Head (or Head and Chest) Injury, (2) Burns, and (3) Fractured Neck of Femur

		(1) Head or Head-chest Injury		(2) Burns		(3) Fractured Neck of Femur	
		No. of Cases	Cases with Venous Thrombosis	No. of Cases	Cases with Venous Thrombosis	No. of Cases	Cases with Venous Thrombosis
A. Survival period (days)	<4	14	3	4	1	2	0
	4–7	6	2	6	1	6	6
	8–14	3	2	6	5	13	10
	>14	4	3	17	13	26	23
B. Age-group (years)	<15	1	0	12	4	0	0
	15–45	10	4	8	6	1	1
	46–60	8	2	3	3	0	0
	>60	8	4	10	7	46	38
All patients		27	10 (37 per cent)	33	20 (60 per cent)	47	39 (83 per cent)

survive 2–4 weeks but remain in bed—and then die often with venous thrombosis (Sevitt, 1957). Prolongation of the life of many with severe head injuries by tracheostomy and other means is likely to have a similar effect.

Lower Limb Injury and Thrombosis.—Clinical evidence of thrombosis in a patient with an injury to one lower limb is usually in the same limb; and therefore injury is said to increase the likelihood of thrombosis in the affected limb. The findings among 109 subjects who died after unilateral fracture of the femur or tibia do not support this (*Table X*). Thrombosis was generally bilateral, involving both limbs in 62 per cent of the cases. Unilateral thrombosis was much less common and was as frequent in the uninjured as in the injured limb. *Table XI* is an attempt to analyse the *extent* of thrombosis statistically; a thrombosis score of 0, 1, 2, 3, or 4 was given to each limb in a predetermined way, but the total scores among the injured and uninjured limbs were much the same. This analysis was restricted to those without loss of thrombi by pulmonary embolism.

Table X.—VENOUS THROMBOSIS AT NECROPSY RELATED TO THE SIDE OF INJURY OF THE LOWER LIMB

	Cases with Venous Thrombosis in				
	Injured Limb only	Opposite Limb only	Both Limbs	Neither Limb	Total
Cases without pulmonary embolism	6	10	25	13	54
Cases with major pulmonary embolism	9	3	43	0	55
All cases	15	13	68	13	109

Table XI.—EXTENT OF VENOUS THROMBOSIS AT NECROPSY IN INJURED AND UNINJURED LIMBS

No. of Cases with Venous Thrombosis and without Pulmonary Embolism	Total Thrombosis Score* (points)	
	Injured Limbs	Opposite Limbs
41	78	83

* Score of 0, 1, 2, 3, or 4 given to the thrombosis in each limb according to its extent.

The undoubted clinical association of trauma and thrombosis on the same side requires an explanation. Limb swelling often begins after a patient is sat out of bed; then the precipitating cause is the dependent position of a limb which is both immobile from injury and thrombosed. This does not explain the onset of swelling during uninterrupted bed-rest, but this is much less common (*see below*) and physiotherapy may play a part.

Diagnosable (Clinical) Thrombosis and Silent Thrombosis.—Unilateral swelling of the limb often beginning in or restricted to the calf is the most reliable sign (*Fig.* 550), but in many cases diagnosis has to be made on minor swelling. Unequivocal spontaneous pain or tenderness in the calf and a definite Homan's sign are of value and may be early symptoms, but they are often absent, particularly in the elderly. A sensation of tightness in the calf is sometimes useful as an early symptom.

Clinico-pathological correlation shows that deep vein thrombosis is symptom-free in the majority of cases (nearly 2 out of 3) and in most of the limbs (about 3 out of 4), even to the most watchful observer. Nevertheless clinical signs are more frequent than is generally believed, and were found in 29 per cent of 150 cases with a fractured neck of femur. *Table XII* compares the frequency of diagnosis during life with that found at necropsy in the special series of patients with fractured hips. Thrombosis was diagnosed in only 40 per cent of the 32 cases with significant thrombi at (+, ++ or +++) necropsy, whilst the remaining 60 per cent were symptom-free. Division into those with and those without pulmonary embolism shows that thrombosis was usually silent whether or not embolic detachment occurred.

FIG. 550.—Swelling of the left lower limb due to deep vein thrombosis. At necropsy the patient had extensive bilateral thrombi in the femoral and iliac veins extending up into the inferior vena cava. In most cases of diagnosable thrombosis the swelling is much less marked and is often of a minor degree.

The extent of thrombosis is an important factor in producing symptoms. Eleven out of 13 diagnosed cases died with either extensive confluent (+++) thrombosis of the leg and thigh veins (9 cases) or non-confluent thigh and leg vein thrombosis (++). In at least 1 of the remaining 2 cases the thrombosis found at necropsy (±) could never have produced symptoms, but in this case there was a long interval (9 weeks) between the clinical attack and death, so that thrombolysis had probably occurred. Extensive thrombosis is not necessarily enough; leg and thigh vein thrombi (++ or +++) were present in 18 out of 24 of those which had been symptom-free. Indeed, 5 of the 14 cases with +++ thrombosis failed to

develop symptoms or signs. It is important to recognize that thrombi are not necessarily completely obstructive even when extensive; they must often float freely in the middle of the venous stream unattached except here and there at valve cusps and vein junctions. (*Table XIII.*)

It was often noted that unilateral swelling of the leg appeared first after a patient was sitting out of bed or after beginning ambulation. Presumably swelling was prevented by the horizontal position of the limb in bed and was precipitated by the dependent position. If this explanation is valid clinical signs of thrombosis should be less frequent in those undergoing prolonged bed-rest than in those with a short incidence of clinical thrombosis (12 per cent of cases) in the non-operated group than in the operated group (32 per cent). The difference was present among those who survived and those who died. Yet at necropsy both groups had a high incidence of deep vein thrombosis (and pulmonary embolism). Thrombogenesis seems to have been equal. Post-operative dependence of the limbs and ambulation presumably permitted a much larger proportion of those with thrombi to develop clinical swelling. This can be explained on morphological and mechanical grounds. In the horizontal position of bed-rest, thrombi can elongate somewhat in the direction of the blood-flow because their attachments are small and few; by becoming less wide they permit onward flow of blood around them. In the vertical position, on the other hand, the thrombi become shorter, squatter, and wider owing to gravity and may block the vein more fully; now the venous flow has to overcome both gravity and the increased resistance of a wider thrombus.

Table XII.—Frequency of Clinically Silent Thrombosis and Clinically Diagnosable Thrombosis

(Number of cases of venous thrombosis diagnosed clinically, not diagnosable clinically (silent thrombosis), and found subsequently at necropsy among 41 specially studied cases with fractured necks of femur.)

	Total Cases	(1) Thrombosis Diagnosed Clinically	(2) Thrombosis* at Necropsy	Silent Thrombosis (2) minus (1)
Cases without pulmonary embolism at necropsy	17	4	11	7
Cases with pulmonary embolism at necropsy	24	9	21	12
All cases	41	13	32	19

* +, ++ or +++ thrombosis (excluding ± thrombosis) (*see* footnote, *Table XIII*).

Table XIII.—Extent of Venous Thrombosis at Necropsy related to Clinical Thrombosis and Silent Thrombosis among 37 Carefully Studied Cases of Fractured Necks of Femur

Cases with	Total No.	Extent of Venous Thrombosis at Necropsy			
		±	+	++	+++
Clinical thrombosis	13	1[a]	1	2	9
Silent thrombosis	24	4	2	13	5

±, Small unimportant thrombi in a valve cusp of a femoral vein (*Fig.* 549) and or in a calf vein.

+, Significant thrombosis confined to the veins of the leg.

++, Thrombosis in leg and thigh veins.

+++, Confluent thrombosis between leg and thigh veins.

The extent of thrombosis recorded refers to the affected limb in those with clinical thrombosis and to the limb with most extensive thrombosis in those with silent thrombosis.

[a], exceptional case. Long interval (67 days) between clinical attack and death, so that extensive thrombolysis may have occurred.

Table XIV.—Precipitation of Clinical Thrombosis by Post-operative Rising and Ambulation

(Note: (1) The high incidence of thrombosis at necropsy among both operated and non-operated cases; and (2) The greater frequency of *clinical* thrombosis among the operated cases (early mobilization from bed) compared with non-operated group (prolonged bed-rest). All the patients were elderly, had a fractured neck of femur, and were the 'control series' in the prophylactic anticoagulant trial (*see* Sevitt and Gallagher, 1959).)

	Total Cases	Clinical Venous Thrombosis			Venous Thrombosis at Necropsy	No. of Deaths	Cases of Fatal Embolism
		Total No.	Among Survivors	Among those who Died			
Operated cases (early post-operative rising and ambulation)	125	40 (32 per cent)	29 per cent	39 per cent	88 per cent	33	12
Non-operated cases (prolonged bed-rest)	25	3 (12 per cent)	12 per cent	11 per cent	63 per cent	9	3
All cases	150	43 (29 per cent)	29 (27 per cent)	14 (33 per cent)	83 per cent	42	15

period of bed-rest but sufficiently long to allow thrombi to form. *Table XIV* suggests that this is so. One hundred and fifty elderly patients with fractured hips are divided into two groups—those operated on (hip-nailing or pinning), usually within a day or two of injury, and those who were not operated on, mostly because they were unfit (their higher death-rate is not surprising). The non-operated cases were kept in bed with the leg in traction for many weeks, whilst the others were generally lifted out of bed within a few days of operation and began supported ambulation within a week or two. The table shows a much lower

PULMONARY EMBOLISM

The outcome depends to a large extent on the length, calibre, and number of emboli; the reactions of the pulmonary vessels and of the heart are also of

great importance, but cannot be considered here. A long wide-calibre thrombus is most dangerous and most fatal emboli come from the iliofemoral channel. The smaller and narrower emboli which commonly arise from the posterior tibial or other calf veins are rarely fatal unless they are multiple and shower both lungs.

Morbid Anatomy.—Emboli are conveniently divided into major and minor kinds.

Major Embolism.—The morphology was adequately recorded in 81 of the 87 cases and divided the fatal emboli into three main groups: (1) A large embolus straddling the bifurcation of the pulmonary artery (*Fig.* 551) or blocking both main arteries at the hila (37 cases). (2) A large embolus in one main pulmonary artery or within two or more lobar branches (29 cases). (3) Multiple small emboli within central and peripheral arteries of both lungs (15 cases).

Infarction was present in 28 cases; sometimes it was obviously recent and related to the attack of embolism, but in others it was older and related to previous embolism. Abscess formation was found in 5 of the 28 cases with infarcts.

1, 2. The great majority of the large emboli were of wide calibre, usually 1·0 to 1·5 cm. in diameter, as if they had originated in a large vein. They varied in length from 5 cm. to 50 cm., but were commonly 10–30 cm. long. The long thrombi were often bent, coiled, or broken into several pieces, presumably during the passage through the heart. Often much of it straddled the bifurcation and extended into main arteries (*Fig.* 551) and sometimes a part was also in the conus pulmonare. In other cases the emboli either blocked one main artery at the hilum or were found in lobar branches; sometimes the main artery was blocked in one lung and lobar branches in the other. Death was usually sudden (51 out of 66 cases), but other syndromes occurred (*Table XV*).

3. The multiple emboli in central and peripheral arteries were mostly short and narrow, 2–5 mm. in diameter and 1–3 cm. long, but often one or more of medium calibre (0·5–1·0 cm.) were also present. Sometimes death was sudden, but more often other syndromes occurred (*Table XV*).

FIG. 551.—Coiled thrombo-embolus straddling the bifurcation of the pulmonary artery and extending into the main right and left arteries.

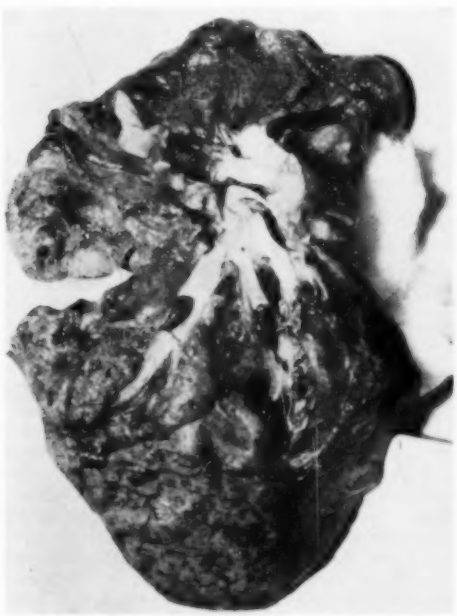

FIG. 552.—Two 'incidental' thrombo-emboli in central branches of the pulmonary artery.

FIG. 553.—A small 'incidental' embolus in a peripheral branch of a pulmonary artery.

Minor Embolism.—This was either: (1) One or two pieces of wide or medium-bore thrombus blocking a lobar artery or main branches (*Fig.* 552)—

hæmorrhagic infarction was occasionally present; or (2) One or a few fine-calibre thrombi lodged centrally or peripherally in the lungs (*Fig.* 553)—infarction was never found. In most cases the embolism was apparently a silent event and without clinical significance.

Minor embolism only was present in 17 of the 104 cases (16 per cent) and previous minor embolism in at least 14 of the 87 cases with major embolism. The real incidence was probably higher, because it can be difficult to distinguish in time of onset small, recent emboli from that causing death, especially when death has been delayed for a few days.

Table XV.—Mode of Dying related to Character of Pulmonary Embolus

Mode of Death	Pulmonary Emboli			Totals
	Bifurcation-embolus or Large Emboli in Both Main Arteries	Large Embolus in One Main Artery, or in One or More Lobar Branches	Multiple Small Emboli (Central and Peripheral)	
Sudden collapse and death in minutes or hours	33	18	4	55
Gradual deterioration over days	3	5	7	15
Respiratory (pneumonic-like) for 1 to several days before death	—	3	2	5
Acute congestive cardiac failure and death days later	1	—	2	3
Acute hypotension and death days later (renal failure, 2 cases)	—	3	—	3
Totals	37	29	15	81

Numerals refer to numbers of cases.

Secondary Thrombosis.—This was not uncommon, particularly with wide-calibre emboli; it varied in amount and usually extended distally from the embolus sometimes into two or more tree-like branches. Occasionally central propagation (against the blood-flow) was found. Secondary thrombosis was found when death after embolism was delayed for hours or longer.

Clinical Syndromes of Embolism.—Not infrequently major embolism is discovered at necropsy, although it is unsuspected during life. This is because it can produce a variety of clinical pictures, but sometimes clinical diagnosis is impossible. Major embolism was found associated with five main syndromes (*Table XV*).

1. *Sudden Collapse and Death.*—This, the well-known picture, occurred in 55 of the 81 cases (68 per cent) in which data were available. Death usually followed collapse within a few minutes or within an hour or two, but sometimes it was delayed for 12–24 hours or even longer. The clinical picture was that of acute asphyxia (cyanosis, respiratory distress), or acute cardiovascular 'shock' (pallor, hypotension, sweating, tachycardia, and polypnœa), or a cerebral episode (coma, convulsions), or a variable mixture. Acute pain in the chest occasionally occurred and led to a diagnosis of coronary occlusion. Large emboli at the bifurcation or in the main arteries were found in most cases (51 out of 55), but in a few (4 cases) multiple small emboli were responsible.

2. *Gradual Deterioration.*—In 15 cases, most of them elderly, there was a period of gradual deterioration over days before death resulted. Embolism was not diagnosed clinically and death was attributed to bronchopneumonia or cardiac failure. Large wide-calibre emboli were present in 8 cases and multiple small emboli in the other 7. Sometimes bronchopneumonia was present and no doubt contributed to death.

3. *Pneumonic-like or Acute Respiratory Syndrome.*—Five cases were characterized by a period of dyspnœa, pyrexia, tachycardia, sometimes cyanosis, and variable signs in the chest. Pneumonia was diagnosed, but death occurred in a few days in spite of antibiotic therapy. Large emboli were present in 3 cases and multiple small emboli in the other 2 cases.

4. *Acute Congestive Cardiac Failure.*—Three cases had an acute onset of congestive cardiac failure with orthopnœa, distended neck veins, and tachycardia, and death occurred 7–15 days later in spite of digoxin therapy. In 1 case large emboli were present in the main hilar arteries, whilst multiple small emboli were present in the other 2 cases.

5. *Acute Hypotension, possibly with Renal Failure.*—In 3 patients an unexpected hypotension of acute onset lasted 12–24 hours and death followed within a few days. At necropsy large emboli in a main or major artery were found, and in 1 case also extensive infarction with early abscess formation. In 2 patients hypotension was followed by acute renal failure, severe oliguria in one and non-oliguric uræmia (Sevitt, 1959a) in the other. Kidney failure was probably precipitated by prolonged renal vasoconstriction following the post-embolic fall in cardiac output, and by the hypotension. Embolism is one of the causes of delayed uræmia in injured patients (*see* Sevitt, 1959b).

Time of Embolism.—The day of embolism could be dated in 83 of the 87 fatal cases by correlating the clinical picture and the time of death with the emboli found at necropsy (*Table XVI*). Five per cent of the datable cases occurred during the first 4 days and 22 per cent during the first week after injury. The number of cases in the second half of the first week

after injury rose sharply and was maximum between 5 and 14 days (43 per cent of cases). Nineteen per cent of the cases occurred during the third week and 13 per cent in the fourth week. After a month there were relatively few cases, presumably because the older thrombi by now had lysed or were becoming organized to the walls of the veins. Fresh extension of thrombi, often the result of consequential bed-rest, were responsible for the 19 per cent of the embolic attacks during the second, third, and occasionally even the fourth months after trauma.

Table XVI.—Day of Onset of Fatal Embolism

Injury to Pulmonary Embolism (days)	Fatal Embolism (No. of cases)
<4	4
5–7	14
8–11	9
12–14	13
15–21	16
22–28	11
29–35	6
36–42	3
57–70	4
>70	3
Not datable	4
Total	87

Some of the later cases happened after discharge from hospital—at home, in private nursing homes, or when re-attending hospital for rehabilitation or other therapy; 6 were traced from the records of H.M. Coroner, but other undiagnosed cases may have occurred.

Origin of the Emboli.—

Thigh or Calf Veins.—The origin of embolism was assessed in 74 cases: 61 came from iliofemoral veins, 11 from calf veins, and 2 from the inferior vena cava. In the others it was not possible to specify the origin. When wide calibre and long total length of embolus indicated a large vein origin, the finding of one empty iliofemoral vein, perhaps containing fragments of thrombus, indicated that it was the vein of origin, especially when thrombus was extensive in the pelvic or thigh veins of the opposite limb (*Fig.* 547). Long emboli may have come from one or both limbs when both iliofemoral veins were empty or partly filled. Multiple small, narrow emboli suggested a small vein origin; thrombi in calf veins had probably been responsible when the thigh veins were empty and some calf veins thrombosed. Sometimes the popliteal or femoral veins of both limbs were also thrombosed and the small emboli may have come from thrombi in thigh veins. The possibility of post-embolic thrombosis or re-thrombosis of veins, particularly thigh veins, raised difficulties, especially when death after detachment had been delayed.

The Silent-thrombosed or Clinically Thrombosed Limb.—Either limb is equally likely to provide the embolus when unilateral clinical thrombosis is present. This is understandable because thrombosis is usually bilateral in cases of embolism (*Table VIII*) and bilateral iliofemoral thrombosis is often present. This is contrary to the general belief that emboli always arise from the clinically affected limb. In 11 cases of major embolism the sides of clinical thrombosis and origin of the embolus could be correlated; the embolus came from the clinically thrombosed limb in 5 cases (iliac or femoral vein), from the clinically normal limb in 4, in 1 case from both limbs, and in 1 case from the inferior vena cava.

Injured or Intact Limb.—Embolism is more common from the veins of the injured limb than from the intact one, but detachment from the latter is not infrequent. In 22 cases of embolism of iliofemoral origin in patients with unilateral lower-limb fractures, the embolus came from the injured limb in 13, from the intact limb in 7, and in 2 cases from both thighs.

Frequency of Embolism.—Reported estimates are either clinical ones based on a large number of patients or are pathological ones based on a series of necropsies. Each is valuable but not comparable with the other unless one series includes the other. In the present investigation embolism was formed in 20·3 per cent of 468 necropsies with injuries and in 5·5 per cent of 163 necropsies with burns (*Table I*). In about four-fifths of the cases (84 per cent) the embolism was major and was judged to have been the sole cause or to have seriously contributed to death.

Frequency of Embolism, Nature of Injury, and the Patient's Age.—The incidence in a series of necropsies depends on the proportion of different cases; some injured patients are more at risk than others, whilst many die before venous thrombosis occurs. Embolism was found in 46–60 per cent of cases dying with a fractured femur or tibia and was the commonest single cause of death among them (*Table I*). It was frequent among those dying after a fractured pelvis (27 per cent of necropsies) or a fractured spine (14 per cent), but was less common in those dying after abdominal, thoracic, or cerebral trauma (2·1–5·5 per cent). McCartney (1934) found embolism in 15 per cent of necropsies with a fractured tibia and in 25 per cent with a fractured femur, whilst Golodner, Morse, and Angrist (1945) found 9 cases of embolism among 25 necropsies on elderly patients with fractured hips. This group is of special importance because the injury is common, the population is ageing, and there is a high rate of embolism. Half of the 104 cases of embolism occurred in such patients (*Table XVII*).

Table XVII.—Age and Sex Distribution of 104 Patients with Pulmonary Embolism at Necropsy

Age-group (years)	Males	Females	Both Sexes
0–20	1	0	1
21–40	3	0	3
41–50	4	1	5
51–60	8	4 (1)	12 (1)
61–70	4	15 (4)	19 (4)
71–80	9 (3)	28 (20)	37 (23)
81–	5 (3)	22 (21)	27 (24)
All ages	34 (6)	70 (46)	104 (52)

( ) = Cases with fractured neck of femur.
Note: Cases >50 years = 95; Cases >60 years = 83.

Indeed, 17 of 165 cases with fractured hips (10 per cent) specially studied by Sevitt and Gallagher (1959) died of pulmonary embolism.

The differences in frequency are largely the result of differences in the incidence of venous thrombosis, which in turn mainly depends on duration of bed-rest and advancing age. Those with the highest rates of embolism have the highest rates of venous thrombosis

(*Table I*), but no other generalization is possible because of differences in the frequency of thrombus detachment (*see below*). (Comparison of detachment rates estimated from *Table I* must be done with care because the two series were not identical.) Those who died after a fractured femur, tibia, or pelvis were mostly elderly; they survived and remained in bed long enough for venous thrombosis to develop. Many of those who succumbed to head injuries, burns, and other trauma were young or died within a few days of injury when venous thrombosis was less common or less extensive. Most of the cases with embolism were middle-aged or elderly and most were female (*Table XVII*). Sixty-one per cent were older than 70 years, 80 per cent older than 60 years, 91 per cent older than 50 years, and only 4 per cent were younger than 40 years. The large proportion of elderly females reflects the large number of patients with fractured hips admitted to the hospital.

Unheralded Embolism and Silent Thrombosis.—About half the cases of fatal embolism occur in patients without *clinical* thrombosis. In the fractured hip series there were 8 cases of fatal embolism in patients who had or had had clinical evidence of thrombosis and 9 cases of unheralded embolism (Sevitt and Gallagher, 1959).

Frequency of Embolism in Patients with Clinical Thrombosis.—The risk of embolism is very high when the thrombosed limb becomes painful or swollen although the embolus often originates from the other limb. In the fractured hip series, fatal embolism occurred in 7 of the 27 untreated cases of venous thrombosis (25·9 per cent) and in 1 of the 16 cases treated with phenindione. Analysis of the literature by Zilliacus (1946) and Bauer (1946) indicates that fatal embolism occurs in 15–25 per cent of cases with diagnosed thrombosis following surgical operation or complicating medical disease and in 3–5 per cent of cases following parturition. The true incidence was probably greater because often embolism can only be diagnosed at necropsy.

Frequency of Embolism in Patients with Silent Thrombosis.—This can only be estimated indirectly and has not previously been reported. In the fractured hip series fatal embolism occurred in 9 of 122 patients* without clinical thrombosis (7·4 per cent) as compared with 25·9 per cent of those with clinical thrombosis. The lesser frequency of embolism is not due to a substantial difference in the incidence of venous thrombi because indirect calculation indicates that most of those without clinical thrombosis, including survivors, had in fact developed thrombosis. The necropsy frequency of silent thrombosis was 70 per cent (19 of 28 cases, *Table XII*); whilst the rate of *clinical* thrombosis among those who died (33 per cent of 42 deaths; bottom row, *Table XIV*) is not dissimilar to that among those who survived (27 per cent of 108 cases, *Table XIV*). This suggests that the frequencies of thrombus formation in survivors and those who died are comparable. If this is so, about 70 per cent of survivors without clinical thrombosis had silent thrombosis. Seventy per cent of 118 survivors* is 83 cases and among these there were 9 cases of fatal embolism. This rate (10·8 per cent) is less than after clinical thrombosis, but it is still not inconsiderable.

Thrombus-detachment Index.—A thrombus-detachment index (T.D.I.) also estimates the risk of embolism from thrombi and is calculated from the frequencies of pulmonary embolism and deep vein thrombosis in an unselected series of necropsies.

$$\text{T.D.I.} = \frac{\text{No. of cases with embolism in the series}}{\text{No. of cases with venous thrombosis}}$$

The index is different from the rate of embolism among a series of patients with thrombosis because that also includes survivors.

The index from iliofemoral (or femoral) thrombi is of most use because these thrombi account for most fatal cases. The index varied in different groups of patients. It was very high (50 per cent) in those dying after a fractured hip and was greater among those who had had clinical thrombosis (60–65 per cent) than among those with silent thrombosis (35–40 per cent), which is in agreement with the greater rate of embolism in the former group. The iliofemoral thrombus-detachment index was significantly lower among burned patients and also among those with a head or head and chest injury (20–30 per cent).

DISCUSSION

Venous dissection of the lower venous tree in patients dying after injury and burning has shown that thrombosis in deep veins is very common and is generally bilateral. The overall frequency of thrombosis in those without pulmonary embolism was 65 per cent, but the actual incidence in any series of necropsies depends mainly on the age-distribution of the cases and the previous periods of bed-rest. The frequency is particularly high in middle-aged and elderly patients who are put to bed for more than 3 or 4 days, and reaches 75–90 per cent in those dying during the next few weeks. It is noteworthy that the nature of the injury has little or no direct influence on the incidence of thrombosis; its influence is indirect and is mediated through age, survival period (bed-rest), and prolongation of life by therapy. The overall frequency in civilian practice is likely to be high because elderly patients form a large proportion of the deaths.

Correlation of clinical signs of thrombosis during life with subsequent necropsy findings has shown that deep vein thrombosis is symptom-free in about 2 out of 3 cases and in about 3 out of 4 limbs. This frequent silent thrombosis explains why so many cases of pulmonary embolism are unheralded by swelling, pain, or tenderness in a lower limb; why fatal embolism continues to be frequent even though therapy with anticoagulant drugs of diagnosed cases of thrombosis greatly reduces the risk in them; and why prophylaxis against thrombosis with phenindione or other anticoagulants is necessary to prevent the unheralded cases of pulmonary embolism (*see* Sevitt and Gallagher, 1959).

Thrombosis was most frequent in the veins of the calf, was almost as frequent in the iliofemoral veins, and was less frequent in the popliteal vein. The distribution of thrombi varied considerably from case to case and often between the two limbs of the one individual. Analysis of the patterns of thrombosis indicates that thrombi *begin* to form at one or

* Control cases and phenindione-reject cases included (*see* Sevitt and Gallagher, 1959).

more of six independent sites, 4 in the thigh and pelvic veins and 2 in the veins of the calf (*Fig.* 544). Extension of thrombosis then occurs from these by propagation or retrogradely, probably after occlusion or near-occlusion of the lumen. The anatomy of the lower venous tree and the dynamics of a slowed blood-flow decide where thrombi begin to form—when the body is in the horizontal position of bed-rest. The soleal veins form a number of intramuscular arcades which increase in number and in lumen diameter with advancing age; thrombosis is facilitated when these become distended with stagnant blood (Gibbs, 1957). The popliteal vein may be compressed at the adductor ring from the bulk of overlying muscle, thus favouring thrombosis at its proximal end; posterior tibial vein thrombosis is possibly encouraged by the relationship of the vein to the upper edge of the soleus muscle; whilst the deep intramuscular location of the profunda femoral vein and pressure from the overlying adductor muscles helps to slow its venous stream. The inguinal ligament facilitates thrombosis in the common femoral because the vein may be compressed particularly when the thigh is flexed on the trunk as in Fowler's position. Eddying of the stagnant flow of blood, with consequent local silting of platelets and leucocytes on to endothelium, probably plays a part in initiating thrombosis at least in the thigh and pelvic veins. Eddying and silting is likely to occur at valves and mouths of vein junctions at the terminations of the profunda femoral, medial, and lateral circumflex veins and other tributaries of the common femoral vein. Above the inguinal ligament eddying and silting may initiate thrombosis in the external iliac vein because, when the body is horizontal, there is an acute weir-like change in direction of the (slowed) column of blood. Thrombosis is more common in the left limb than the right, particularly in the left thigh, and it is likely, as Aschoff (1924) noted, that this is because the left common iliac vein is compressed by the origin of the left common iliac artery.

The findings support the old contention that venous stasis plays the major aetiological role in venous thrombosis. Emptying of veins depends on muscle contraction, and lack of this, particularly in the elderly, will allow the blood to become stagnant. The common denominator of venous thrombosis is venous stasis; and, in addition to the peculiarities of venous anatomy in the lower limbs which determine the primary location of thrombi through eddying and silting of the flow, the major roles are played by age, immobility, and, above all, bed-rest. The reason for confinement to bed is less important.

The factors influencing the onset of clinical signs of thrombosis are complex, but dependence of the limbs and the effect of gravity on thrombi and on a venous flow already handicapped by thrombi play an important part in bringing about swelling. Swelling of the calf often first appeared after a patient had begun to sit out of bed or when beginning to walk; whilst in those with fractured hips clinical evidence of thrombosis was less common in those undergoing prolonged bed-rest than in patients who began ambulation within a week or two of injury.

Pulmonary embolism at necropsy was common after trauma (20·3 per cent) and was less common after burns (5·5 per cent); in the great majority of cases it was judged to have caused or seriously contributed to death. The necropsy incidence corresponds to about 0·7 per cent of patients admitted for longer than 24–48 hours to the Birmingham Accident Hospital, that is excluding patients 'detained' in the short-stage wards attached to the casualty department. The true incidence is greater because undiagnosed cases which died but were not necropsied and clinical cases among survivors are not included. A more accurate estimate is now being attempted, but the present data indicate that the incidence of fatal embolism is about 1 per cent of the in-patients and the overall incidence (fatal and non-fatal) about 2 per cent. The literature on embolism after injury is limited, but it also indicates a high risk. McCartney (1934) found embolism in 3·8 per cent of over 1600 necropsies with trauma, and Hamilton and Angevine (1946) found it in 6 per cent of over 1000 necropsies on battle casualties, many of them with injuries to the lower limb. Among medical and general surgical necropsies the rate ranges from 2·6 per cent (McCartney, 1934), 6 per cent (Cohn and Walsh, 1946), 9–14 per cent (Belt, 1934; Hampton and Castleman, 1940; Gibbs, 1957), 17 per cent (Hunter and others, 1945) to 23 per cent in an institution for chronic sickness (Moran, 1947). Of course the frequency at necropsy also depends on the vigilance and technique of the pathologist, and concurrent studies are the most valuable. Clinical estimates in non-traumatic cases vary from 0·03 per cent to 0·7 per cent, but they all err on the low side because of difficulties in diagnosis. Bauer's (1946) summary of recorded fatal embolism was 0·26 per cent after surgical operations, 0·4 per cent in medical cases, and 0·033 per cent after parturition. In other series, mainly surgical cases, the figures are 0·085–0·14 per cent (Kistner and Smith, 1954), 0·19 per cent (Jorpes, 1947), 0·24 per cent (Wise, Loker, and Brambel, 1949), and 0·7 per cent (Barker, Cromer, Burn, and Waugh, 1945). (*See also* Zilliacus, 1946; Gjores, 1956.)

Nearly half the present cases occurred within 2 weeks of injury, 30 per cent during the third and fourth weeks, but cases continued to occur during the second, third, and even the fourth months, sometimes at home or in private nursing homes after discharge from hospital. The connexion between embolism after discharge and the previous injury may be important medico-legally (e.g., for insurance purposes), but more important is to avoid the misguided good intentions of relatives or attendants who may put to bed a patient reasonably mobile on discharge, thereby permitting further thrombosis to occur.

Thrombosis in deep veins was found in all cases with embolism, so that there is no necessity to postulate primary thrombosis of the pulmonary arteries to explain the pathological findings.

The frequency of embolism among patients dying after different injuries varied considerably, but this largely depended on survival period and age; the highest rates of embolism were in patients with a high incidence of thrombosis, and these were the middle-aged and elderly patients who survived and remained long enough in bed for thrombosis to develop. The risk of fatal embolism in elderly patients with fractured hips was high (25 per cent) when there were clinical signs of thrombosis; whilst it was lower, but still considerable (10 per cent), in those with silent

thrombosis. About half the fatal cases were in patients without warning signs in the lower limbs. This unheralded embolism probably explains the experience of Marks, Truscott, and Withycombe (1954), who found that the annual number of cases of fatal embolism was apparently unaffected even though they had treated more than 1000 cases of clinical thrombosis with a very low mortality.

Pulmonary embolism is often difficult to diagnose clinically, and many cases were found at necropsy which were unsuspected during life. Therefore clinical estimates of the frequency of embolism err on the lower side. The manner of death varies and, in addition to the classical syndrome of sudden collapse and rapid death, other pictures are gradual deterioration (more likely in the elderly), a pneumonic-like syndrome, acute congestive cardiac failure, and a sudden attack of hypotension possibly resulting in acute renal failure. The variable clinical picture which follows sudden collapse or during the delay before death occurs probably stems from the complex changes which follow major embolism. These are reduction in cardiac output with consequent reduction of systolic blood-pressure, and hence cerebral blood-flow, and production of renal vasconstriction; acute right ventricular and pulmonary hypertension; the blockage of pulmonary flow; consequent reduction of venous return; and possibly infarction. When death is delayed one or other group of effects may be maintained or predominate. Pathologically, major embolism is classified into large emboli blocking the pulmonary artery or its main branches, a large embolism in one or more lobar branches and multiple small emboli within smaller pulmonary arteries. Secondary thrombosis, which usually extends the embolus distally, was not uncommon, particularly when death was delayed. Its importance is that it may help to determine a fatal outcome in cases balancing between life and death, and its prevention is probably the basis of urgent therapy with intravenous heparin. Diagnosis of embolism should therefore be made as soon as possible. Minor embolism was not infrequent and was also found in cases without major embolism; in many cases it was an incidental, clinically silent event. The majority of fatal emboli come from an iliac or femoral vein and not from calf veins as is believed by many clinicians. Either limb is likely to provide the embolus when unilateral clinical thrombosis is present because the thrombi are bilateral; but, in patients with injury to one lower limb, thrombi from the injured limb provide the emboli in about two-thirds of the cases.

Clinical factors other than age and duration of bed-rest which may influence the frequency of venous thrombosis and embolic detachment are at present being studied. Suffice it to say at present that in the fractured hip series embolism was more frequent in those operated on later than 3 days after injury than in those operated during the first 2 days; obesity probably predisposes to a higher rate; poor general health, reduced ambulation before admission, congestive cardiac failure, and hypertension are possibly, but not certainly, associated with a higher rate of embolism.

SUMMARY

At necropsy, deep vein thrombosis in the lower venous tree was found in 65 per cent of 125 subjects (without embolism) dying after injury or burning. Pulmonary embolism was present in 20·3 per cent of 468 necropsies after injury and in 5·5 per cent of 163 after burns; in the great majority it caused or seriously contributed to death. More than 1 per cent of patients admitted to the Birmingham Accident Hospital have died of pulmonary embolism. All the patients with pulmonary embolism had deep vein thrombosis. Venous thrombosis is mainly related to age and survival period (bed-rest), and its frequency is particularly high (75–90 per cent) in middle-aged and elderly patients who die after having been confined to bed for more than a few days. The highest necropsy frequencies of embolism (46–60 per cent) were in those dying after a fractured femur or tibia, mainly because these are middle-aged and elderly subjects who survive long enough for deep vein thrombosis to develop. The nature of the injury has little direct influence on thrombosis. Thrombi were usually bilateral when present, even in cases with unilateral lower limb injury, but in most cases they were symptom-free. Thrombosis can occur independently in veins of the calf, thigh, and pelvis, but thrombi in the calf veins and in the iliofemoral channel are most frequent. Various combinations of thrombosis occur; these indicate that thrombi *begin* to form in one or more of 6 independent sites, viz.: soleal veins, posterior tibial veins, popliteal vein, deep femoral vein, common femoral vein, and the iliac vein, usually the external iliac. Venous stasis from recumbency, immobility, and age together with the peculiarities of venous anatomy decide where thrombi begin to form.

Nearly half of the cases of pulmonary embolism occurred within 2 weeks of injury, but fatal embolism continued to happen for 3 or 4 months. Many cases were unsuspected during life so that clinical estimates of frequency err on the lower side. Various clinical pictures of fatal embolism were revealed by a clinico-pathological study of a special series with fractured hips, viz.: sudden collapse and death, gradual deterioration, a pneumonic-like syndrome, acute congestive cardiac failure, and acute hypotension. The risk of fatal embolism in those with diagnosable thrombosis was about 25 per cent (although the emboli often came from the other limb), and about 10 per cent in those with silent thrombosis. Half the cases of fatal embolism are not preceded by warning signs in the limbs and this indicates the necessity for prophylaxis with anticoagulant drugs against venous thrombosis and hence pulmonary emlbolism.

Acknowledgements.—One of us (S. S.) is a part-time member of the Scientific Staff of the Medical Research Council. We are grateful to our clinical colleagues for their interest and co-operation, and to Mr. R. Gill and Mrs. V. Montague-Smith for photographic assistance.

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THE EPICHOLEDOCHAL VENOUS PLEXUS AND ITS IMPORTANCE AS A MEANS OF IDENTIFYING THE COMMON DUCT DURING OPERATIONS ON THE EXTRAHEPATIC BILIARY TRACT

BY JAMES H. SAINT*

THE literature is replete with sound advice to the surgeon who essays an exploration of the extrahepatic biliary tract, warning him of the difficulties which he may expect to encounter and offering suggestions as to how best they can be avoided or overcome. Notwithstanding such advice, inadvertent injuries to the common bile-duct and common hepatic duct, with their heavy resultant toll of morbidity and sometimes fatal outcome, continue to occur from time to time. On the occasions when such injuries form the topic of discussion among surgeons the term 'common duct', though anatomically perhaps leaving something to be desired, is customarily accepted as embracing both these structures since they form a continuous bile-passage. This terminology will be followed in the present communication, but where there is need for specific reference to one or other of these structures its strict anatomical designation will be used.

Particular emphasis has rightly been laid upon the importance of identifying the local structures, which implies the necessity of a sound working knowledge of the normal and anomalous anatomy of the region as the foundation on which safe surgery is based. Apart from the gall-bladder, usually readily recognizable, the key landmark of this region is the common duct, so that its identification is not only a matter of paramount importance for its own safety but also of considerable help in the recognition of other structures which are in its immediate vicinity. It is obvious that the earlier the duct can be identified at operation the greater will be the confidence with which subsequent steps in the dissection can be undertaken, thus diminishing the chances of possible injury to the duct itself or to adjacent structures.

In the identification of the common duct the authorities in the literature emphasize careful dissection as the basic means of attaining it. However, in cases where the dissection proves to be difficult, there still remains the possibility, not to be ignored, that the duct may be injured while the attempt to identify it is in progress. These authorities also seem to agree that, if bile can be withdrawn through a needle from the suspected common duct, its identification is established beyond doubt. Such an assumption fails to take into account that bile can similarly be withdrawn from a dilated cystic duct which, if coursing parallel to the common duct as it does on occasion, may be mistaken for the latter, an error which could have regrettable consequences before being discovered. It is apparent, therefore, that the usual means employed to establish the identity of the common duct do not always accomplish their objective with either ease or certainty. On the other hand, there is one which does so in the great majority of cases and it forms the subject of this communication.

For many years I have identified the common duct by the presence on it of a fine venous plexus which is in intimate contact with the outer coat of the duct wall (*Fig.* 554). Since this plexus is extramural and is situated on the common duct, its designation as the 'epicholedochal venous plexus' is here suggested as being appropriate for it. Subject to the amount of the duct exposed at operation, the plexus may be observed to extend from the origin of the common hepatic duct above to the point below where the common bile-duct disappears behind the superior border of the duodenum. Hence from the practical standpoint it is fortunate that the plexus is to be found on this supraduodenal portion of the duct which is not only the most accessible but also that with which the surgeon is mostly concerned. The plexus is often fragmentary rather than complete, but I would like to emphasize that the presence of a portion of the plexus constitutes just as positive an identification of the duct as does the whole. The plexus is not usually visible through the intact peritoneum covering the hepatoduodenal ligament, although it may be seen thus on occasions when the subperitoneal fatty tissue is minimal or absent—that is, even before any dissection is begun. However, it becomes apparent as soon as this covering is incised and the medial leaf reflected towards the left to expose the structures lying in the free edge of the ligament. It has been my repeated observation that none of these structures, with the exception of the common

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duct, has a venous plexus on its wall, and especially have I found this to be true of the cystic duct which is the most likely of them to be mistaken for it. Therefore, as soon as the plexus is seen we know that the structure on which it lies *must* be the common duct—it cannot be any other—and so without further hesitation or uncertainty its identification is quickly and positively established.

The veins of the epicholedochal plexus vary in size from about 1 mm. in diameter to a fraction thereof, but, containing venous blood, they are in contrast

FIG. 554.—Line-drawing of the supraduodenal portion of the extrahepatic bile-ducts showing the epicholedochal venous plexus (composite) as observed by the author during operations. It is seen extending from the origin of the common hepatic duct above to the point below where the common bile-duct disappears behind the superior border of the duodenum. Possible variations in the calibre of the veins are indicated. The mesh is wide and the reticular pattern somewhat irregular. The plexus is often fragmentary rather than complete as shown. It was observed cephalad only as far as the origin of the common hepatic duct and is therefore not shown on the right and left hepatic ducts (cf. *Figs.* 556, 557, 559). Note the absence of the plexus on the cystic duct, as is usual.

with the lighter colour of the duct wall and so are usually readily discernible. The reticular arrangement is somewhat irregular and the mesh is comparatively large, the spaces enclosed by the veins often measuring as much as 5–6 mm. in width. Nevertheless, it is obvious that an incision through the duct wall of sufficient length for satisfactory exploration of its lumen ordinarily cannot avoid cutting through one or more of the veins of the plexus. This explains why choledochotomy is nearly always associated with hæmorrhage of the venous type, although a tiny spurter may be encountered if one of the minute arteries supplying the duct has been cut. The bleeding may be of sufficient degree to be troublesome in that it tends to obscure the small but important part of the operative field where it is occurring and may be rather difficult to control. Incision of the cystic duct, on the other hand, is usually not accompanied by hæmorrhage as there is no plexus on its wall to give rise to it. Further, the presence of the plexus warns us to exercise great care when dissecting in close proximity to the common duct as lack of gentleness can easily result in the tearing of one or more of its thin-walled veins. I have never been able to convince myself that pathological conditions in the liver or extrahepatic biliary tract, especially the more common ones of inflammation, acute or chronic, or cirrhosis, are necessarily associated with concomitant changes in the appearance of the plexus. It is possible that conditions such as these mentioned may lead to congestion of the veins of the plexus or to their dilatation, and thereby render them more readily observable. However, such changes in the plexus will always be difficult to determine or evaluate because of the fact that there is no norm by which variables can be measured, for even when the common duct appears normal in all respects the plexus may be more pronounced, and therefore more easily observable, in some cases than in others. It might well be asked, In what percentage of cases is this plexus likely to be observed? I would say in reply that it is most unusual not to find some evidence of its presence.

The advantages accruing from a quick, easy, and positive identification of the common duct during operations on the extrahepatic biliary tract are at once evident. By observing the epicholedochal venous plexus, which will be visible as soon as he has taken the first step of reflecting the peritoneum covering the anterior aspect of the hepatoduodenal ligament, the surgeon, at this early stage of his dissection, enjoys the satisfaction of knowing that he has positively identified the duct and of thus having found a landmark which he can use for the identification of other structures. In this way he is in a position to continue the operation with an assurance which he otherwise might not feel, for the plexus on the common duct helps him to define the duct more clearly, and this in turn makes the dissection of other important structures less hazardous and the discovery of important anomalies more certain. The absence of the plexus on the cystic duct not only enables it to be identified by contrast, but also allows it to be followed unerringly, no matter how devious its course, to the point of junction with the common duct, thus lessening the chances of leaving behind too long a stump on the one hand and of placing a ligature too near the common duct on the other, either of which procedures we know may result in future trouble. In secondary explorations of the extrahepatic biliary tract, in general undertaken because of common duct pathology, often a possible previous cholecystectomy will have removed a useful landmark and the probable presence of adhesions may have resulted in distortion of the normal anatomical relationships, adding to the difficulties with which the surgeon has to contend in his search for the common duct and so increasing the chances of injury both to the duct itself and to important neighbouring structures. Under such circumstances the identification of the duct by observation of its extramural venous plexus may well save much time and trouble. When a stricture of the common duct is present, part of the duct may be completely obliterated or altered to an extent as to be unrecognizable as such. The surgeon is then faced with the now greater problem of having to identify the remaining unimpaired portion of the duct, but he is likely to find that its easiest solution will come from his recognition and

utilization of the plexus. I might mention here that injection studies, to be presented later in this paper, have demonstrated a fact which I have long suspected but never have been able to establish satisfactorily at operation—namely, that the epicholedochal venous plexus extends cephalad on both the right and left hepatic ducts. This knowledge could prove of great importance in the identification of these ducts in cases where the common hepatic duct has been rendered unrecognizable by injury or disease.

No claim is made here that the observation reported in this communication concerning the existence of the epicholedochal venous plexus is an original one. Yet, because of my interest in the plexus and the tremendous help it has been to me on innumerable occasions, I have always been impressed, as well as surprised, by the fact that it does not seem to have been given any recognition, although operations on the extrahepatic biliary tract have been common procedures in surgical practice for more than fifty years. During the time, for instance, that I have been repeatedly demonstrating the plexus to residents and interns at operations, I found that none of them appeared to have previous knowledge of its presence. Furthermore, an investigation undertaken of the various sources which might possibly afford information on the plexus disclosed that no mention of it is made in any of the standard text-books of anatomy (its omission from manuals of dissection is understandable since it is likely to be observed only in the living subject); even more striking was the discovery that it is given no recognition in any of the more numerous books concerned with regional anatomy, such as those written on surgical anatomy and operative surgery. Finally, there remained for consideration the many separate articles in the literature which are devoted exclusively to the surgical and anatomical aspects of the extrahepatic biliary tract and the structures closely associated with it; throughout an intensive review of such articles published since the turn of the century, I did not encounter among them a single reference to, or description of, a venous plexus [*sic*] on the wall of the common duct. Flint (1923), however, in commenting on hæmorrhage which, on opening the common duct, may originate from an artery that sometimes crosses in front of the lower portion of the supraduodenal part of this duct (and one which, at that time, he was seemingly unable to identify) remarks that, "Though a plexus of veins and arterioles is described on the surface of the duct . . .". He omits, however, to indicate where the description of this plexus is to be found, nor does he refer to it again in his paper. In my study of the literature I was unable to find any reference, previous to that of Flint, to "a plexus of veins and arterioles" on the common duct. Friend, in 1929, discussing abnormalities of the bile-ducts and their blood-vessels, states that "Covering the common duct there is a plexus of veins and arterioles". His first figure shows tiny arterioles ramifying on the wall of the common duct and doing so more or less parallel to its longitudinal axis; there is also a small inset illustrating a fine vascular network on the wall of the common and cystic ducts similar in appearance to my drawing of the epicholedochal venous plexus (*Fig.* 554). The article makes no further reference to this plexus of veins and arterioles, nor does its author inform the reader whether his statement concerning the presence of the plexus is based on personal observation or, if not, the source from which he obtained his information. Perhaps Friend intended the inset, mentioned above, to indicate that he was aware of the existence of the venous plexus on the common duct that I have described; if that were so it is unfortunate that he says nothing in the text of his article that could in any way be construed as confirming his possible recognition of the presence of this venous plexus. I would point out that neither Flint nor Friend, both of whom were surgeons of wide experience, suggested the possibility of utilizing the plexus, such as mentioned by them, as a means of identification of the common duct in operative procedures on the extrahepatic biliary tract, although each of their articles was written, as is the present one, in a purposeful attempt to diminish the risks attending such operations by the presentation of supplemental anatomical information likely to prove of help to the surgeon.

Because of the great interest shown in the extrahepatic biliary tract and its adjacent structures by the late Sir David Wilkie, I made an exhaustive inquiry as to whether he had ever written on the subject of a venous plexus on the common duct. I failed, however, to find any reference to it in any of his published papers.

Study of the literature reveals that, while knowledge of the intricate vascular patterns in the region of the pancreas and duodenum has been brought to its present satisfactory level by the commendable contributions of a number of interested investigators, more of these have concerned themselves with determining the arterial supply than with the elucidation of the venous drainage. It shows further that scant attention has been paid to the common duct from the vascular standpoint, although this structure is such an integral part of the region. As a result I find that there are but two investigators, namely, Professors Ture Petren of Stockholm and J. C. B. Grant of Toronto, whose work has enough bearing on the subject of this communication to be of sufficient interest and importance as to commend itself for reference, and their contributions will be discussed forthwith.

Petren in 1932 published his article on the veins of the extrahepatic bile-passages, a presentation of the results of injection of the superior mesenteric vein, carried out in more than 50 cases, after preliminary unsatisfactory experience with the main trunk of the portal vein as the site of injection. I would like to draw attention to two portions of his article. Referring to the first of his two illustrations, he writes: "We see here that the bile-ducts are accompanied by large veins which anastomose with each other as well as with the veins of the gall-bladder. Toward the duodenum and the head of the pancreas they communicate with the veins of those organs." His second illustration is mentioned in the following context: "The hepatic duct and the common duct are usually accompanied by two veins, often of considerable size. In the majority of cases these veins communicate with those of the pancreas and duodenum. They almost invariably empty directly into the liver. This is true in 96 per cent of cases investigated by us. Therefore these veins could suitably be called common bile-duct veins. *Fig.* 555 shows the common

duct veins strongly developed." Several features of the illustrations and text of Petren's article call for comment. In the first place, it would seem that a vein located on the right side of the common duct and of such a large diameter as illustrated would be readily observable during operations on the extrahepatic biliary tract. Yet, in the hundreds of such operations I have performed I never remember having observed it, although it is of much larger calibre than the veins

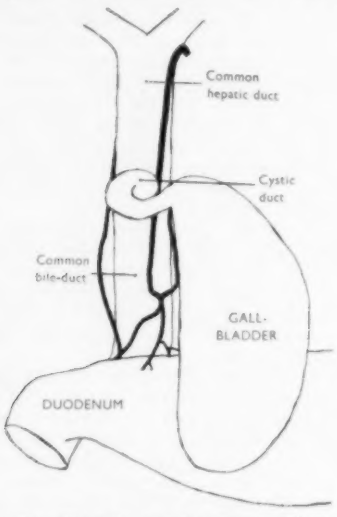


FIG. 555.—The veins near the common bile-duct (*after Grant*). These long, large paracholedochal veins are seen to form a pattern similar to that depicted by Petren (*see* text).

which constitute readily observable epicholedochal plexus. Nor have I ever found any reference to it in the surgical literature. Secondly, the anastomoses between the long veins on each side of the common duct, as depicted in the illustrations, would seem hardly to merit the title of 'plexus' and it is significant that Petren himself does not use this word in connexion with them. Thirdly, the text states that these veins 'accompany' the hepatic duct and the common duct and the illustrations confirm this relationship in that, while the veins are near the duct, they are not in contact with its wall. They are therefore paracholedochal rather than epicholedochal. This is in contradistinction to the veins of the plexus I have described which lie actually on the wall of the duct and in such close contact with it that any attempt to separate them from it will usually result in rupture of the vein walls—in other words, this plexus of veins is essentially epicholedochal and not paracholedochal. From these considerations I feel that there is no choice but to conclude that Petren's illustrations and textual descriptions do not refer to the epicholedochal plexus, described herein, but to a venous pattern present in the region of the common duct and one which, in my investigations, I happened to find present only in a minority of the specimens injected. I realize that it is possible that failure on my part to demonstrate these veins of Petren more frequently may have been due to the limitations inherent in the technique of simple injection, the method used in my studies, and that one of injection-corrosion type might have proved more successful in this regard. On the other hand, I consider it would not be unreasonable to expect that where some portion of the fine veins of the epicholedochal plexus has been filled with the dye, such as occurred in a high percentage of the specimens I injected, these larger veins, if they were present, would also have been outlined with the dye. I would point out that Petren's findings are not without surgical significance, for, should the veins he describes be observed at operation, they should certainly serve to warn the surgeon of his close proximity to the common duct although they do not actually identify this structure as does the epicholedochal plexus.

The fourth edition of Grant's *Atlas of Anatomy* (1956) contains many beautiful coloured drawings of dissected injected specimens. One to which I wish especially to draw attention is Fig. 133.1 (*see my Fig.* 555). Professor Grant tells me that the specimen shown in this illustration was prepared by injecting the hepatic artery and the superior mesenteric vein with red and blue latex respectively and that the veins were largely discarded in order to display more effectively the arteries. However, there still remain two relatively large, long veins, one on each side of the common bile-duct and coursing parallel to its margins, while a third long vein, situated between the two just mentioned and running parallel to them, is also seen, anterior to the duct. Thus the venous pattern in the region of the common duct shown in this illustration is similar to that depicted by Petren. Communications between these veins are seen just above the superior border of the duodenum and they are described by Grant (personal communication) as forming a plexus that occupies several planes. Yet again it is to be noted that these veins and the plexus formed by the communications between them do not bear the intimate relationship to the wall of the common duct that is a characteristic feature of the epicholedochal venous plexus—that is, they lie beside the duct but not actually on its wall and thus are paracholedochal. Later in this paper will be shown photographs and accompanying key drawings of the epicholedochal venous plexus as outlined by injection, affording evidence that it forms a definite anatomical entity quite distinct from the paracholedochal venous pattern described and illustrated by both Petren and Grant.

INJECTION STUDIES

The purpose of the studies, undertaken in the Cottage Hospital Department of Pathology, Santa Barbara, California, through the courtesy of Dr. E. L. Benjamin, was to provide convincing evidence of the existence of the epicholedochal venous plexus and to verify its characteristics as already illustrated (*Fig.* 554) and described in this paper. On several occasions in time past, in attempts to obtain such evidence, I had photographs taken at operations on the extrahepatic biliary tract but all failed to show the plexus satisfactorily. Consequently, up to the time of these studies, the only means I had of showing the appearance of the plexus, apart from the limited opportunities afforded by its demonstration during operations, was to make a drawing of it, this providing evidence of a type that could be claimed by the sceptical as representing no more than a figment of my imagination.

I considered that it should be possible to fill the tiny veins of the plexus, if not completely then at least to an extent sufficient to prove its existence, by means of injection with some sort of medium. Undoubtedly the ideal medium for such a purpose is one which solidifies after being injected and thus permits of a dissection which can be undertaken later at leisure and without fear of leakage of the medium from any injected veins whose thin walls might be accidentally torn. However, because the employment of such a medium involves the expenditure of much time as well as the use of certain facilities which were not available to me, I decided to try instead the simple injection of a coloured fluid, preferably dark, in order that the appearance of the injected plexus should be as similar as possible to that observed in the living subject. After experimenting with the use of ink the medium finally selected was 1 per cent gentian violet, an aniline dye. Later it was found that the dye could be diluted to less than one-quarter of this strength and still outline the veins satisfactorily. From the time of its first use it was evident that the dye was able to penetrate farther than the ink into the venous bed injected and there began to appear encouraging evidence of the presence of the plexus as shown through its partial delineation with the dye.

Each specimen to be injected consisted of the liver and gall-bladder, the stomach, duodenum, and pancreas, and the intact hepatoduodenal ligament, the superior mesenteric vessels having been severed, together with the mesentery, an inch or so below the inferior surface of the pancreas. I found that injection of the main trunk of the portal vein was unsatisfactory as leakage was apt to occur around the needle, resulting quickly in infiltration of the tissues of the hepatoduodenal ligament by the extravasated dye, obscuring its contents and rendering impossible the making of reliable observations. For this reason it was decided to inject a vein at some distance from the ligament, the superior mesenteric being the obvious choice. The terminal 2 cm. or so of the cut end of this vein were dissected free and a syringe adaptor introduced into it and tied securely in position by one or more ligatures of stout thread placed distal to its bulbous tip. Injection of the dye through the adaptor (a 10-ml. syringe was ordinarily used) forced the fluid into the vascular bed consisting of the portal vein and its pertinent tributaries. The carrying out of certain measures was necessary before the specimen was ready for injection. Since my purpose was to fill the plexus, injection of the liver itself was obviously not necessary, so that much of both time and dye were saved by ligation of the right and left branches of the portal vein, this being done as close as possible to the porta hepatis. The remaining steps taken to prepare the specimen were concerned mainly with the prevention of leakage of the dye and were necessary to achieve a satisfactory result. They consisted essentially of a series of ligatures placed in certain locations, namely: (1) around the duodenum just proximal to its cut end; (2) around the body of the pancreas to the left of the axis of the superior mesenteric vein, thus occluding both the splenic and inferior mesenteric veins in a quick and efficient manner preferable to the tedious, time-consuming, and unnecessary alternative of dissecting out each vein before its separate ligation; (3) around the antral portion of the stomach to prevent escape of the dye into the large gastric venous bed through the right gastric and gastro-epiploic veins; and (4) around the loose tissues adjacent to the upper portion of the lesser curvature of the stomach to occlude the left gastric vein for the same reason. In spite of these precautions leakage nearly always occurred from the root of the mesentery through some of the smaller branches of the superior mesenteric vein. It was often impossible to detect these small veins on examination of the specimen, leakage of the dye from them providing the first indication of their presence; accordingly it was of great help to have several hæmostats, preferably curved, readily available just before beginning the injection of the dye so that each point of leakage could be clamped immediately it became apparent, the amount of leakage thus being kept to a minimum. In order to lessen the chances of extravasation of the dye from torn veins into the tissues of the hepatoduodenal ligament, dissection of the extrahepatic biliary ducts was not begun until the injection of the specimen was considered complete. The amount of dye used for injection of each specimen usually varied from 15 to 30 ml., being rarely less than the former figure and practically never greater than the latter. As soon as the dissection of the supraduodenal portion of the extrahepatic biliary ducts was completed, that portion of the specimen was photographed in colour. This method of illustration, while enabling a permanent record to be made of the result of any given injection, is not without its drawbacks. Perhaps the most serious of these is reflection of the high-powered lights, necessary to illuminate the specimen for photographic purposes, from its smooth and glistening surface; such reflection may result in the obliteration of detail, especially that of the finer venous patterns. It was found too, on occasions, that œdema of the tissues, due to the presence of embalming fluid, tended to produce a blurring of the outlines of the injected veins. Because such factors can result in a photograph that may fall short of expectations, I decided to make line-drawings of the injected specimens at the time of photography. Each of these drawings provides a key to the photograph it accompanies and it is hoped that they will prove of interest to the reader by helping him to follow and interpret the photographs should he experience any difficulty in doing so without their aid.

More than 20 specimens were injected, but about half that number were rendered unfit for photography by leakage and extravasation of the dye, this occurrence proving to be the great handicap of employing a medium which remains fluid. In fact it was found to be impossible to do a dissection of the extrahepatic bile-ducts after injection of the dye without some degree of leakage occurring, in spite of all the precautions taken to prevent it, as there are so many veins in the loose connective tissues of the hepatoduodenal ligament. Many of these veins are tiny, however, and leakage from them insufficient to spoil the specimen. On the other hand, I quickly discovered what a surprisingly small amount of leakage from a larger vein is enough to ruin a specimen for photographic purposes, although often before this happened a considerable amount of venous detail could be observed.

RESULTS OF INJECTION STUDIES, WITH COMMENTARY

The results of the injection studies which were undertaken are epitomized in the representative group of colour photographs and line-drawings which were selected to illustrate this article. The accompanying legends call attention to their salient features.

In outlining the plexus these studies provided additional information regarding its extent. *Figs.* 556, 557, and 559 show that the plexus does not terminate above at the point of origin of the common

A B

FIG. 556.—A, The colour film of this specimen was unfortunately developed by mistake as a black-and-white. The epicholedochal venous plexus is well outlined on the common bile-duct and common and right and left hepatic ducts but is absent on the cystic duct. The veins of the plexus on both hepatic ducts ascend to the porta hepatis and enter the liver parenchyma. Note the variations in the calibre of the veins of the plexus. Veins of Petren are not present. The inferior cystic vein disappears behind the common hepatic duct where it was observed to bifurcate, each of its branches terminating in a vein of the plexus on the posterior wall of the duct. Fatty tissue seen overlying the left margin of the common bile-duct was left undisturbed for fear that its attempted removal would result in the tearing of the veins of the plexus lying underneath it and so ruin an otherwise good specimen through extravasation of the dye. B, Key line-drawing of A.

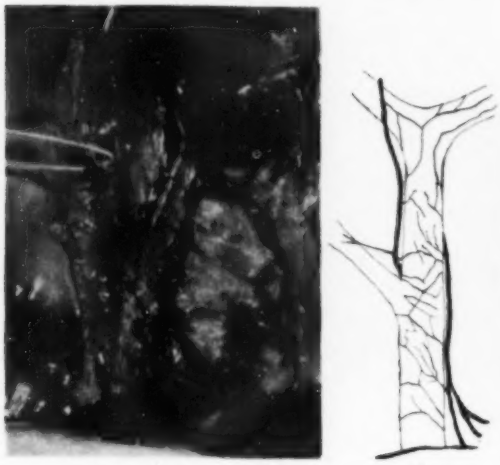
In evaluating these results the main points to be considered are: (*a*) whether or not the studies have verified the clinical observation, reported earlier, that a venous plexus is present on the wall of the common duct and, if they have done so, (*b*) the extent to which the characteristics of the plexus, as outlined by the dye, bear comparison with those of the plexus observed during operations as shown in *Fig.* 554 and described in the text.

A perusal of the illustrations will suffice to settle these points beyond doubt. In the first place, *Figs.* 556–560 provide unequivocal proof that such a plexus is present on the wall of the common duct; while the distribution of the plexus in some instances shows a lack of uniformity that could possibly be due to incomplete filling of its veins with the injected dye, yet this fragmentary appearance of the plexus has already been mentioned as a feature noted not infrequently at operation. Secondly, although the plexus is not so well delineated with the dye in some specimens as in others, yet in all of them its characteristics are seen to be essentially the same as those observed at operation—namely, a comparatively wide and somewhat irregular reticulum of veins, all of small calibre but often varying in size. Moreover, it is obvious from these illustrations that this plexus forms a definite anatomical entity quite distinct from any other similar venous patterns that may be present in the vicinity of the extrahepatic bile-passages.

hepatic duct as illustrated in *Fig.* 554, but is continued cephalad on the walls of the right and left hepatic ducts to the liver parenchyma. Reference has already been made to the significance of this finding as a means of identification of these ducts, especially in secondary operations on the extrahepatic biliary tract. The veins of the plexus on these two ducts are seen to pass directly into the liver parenchyma. It is probable that their intrahepatic behaviour is similar to that of the veins of Petren investigated by that author with stereoscopic radiography and corrosive preparations; he found that these veins as a rule ramify quickly into capillaries and only seldom empty into a branch of the portal vein.

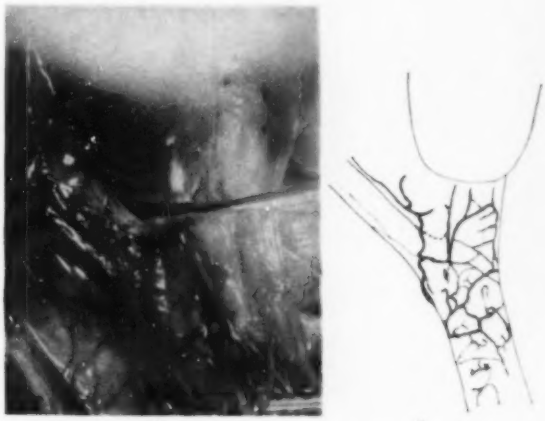
As would be expected, the plexus communicates with other veins. The long veins of Petren, when present, are connected with it at intervals along their course (*Figs.* 557, 560). In several specimens the inferior cystic vein drained into the plexus as shown in *Figs.* 556, 559, dividing into two or more terminal branches before doing so, and in another specimen it was seen to be connected with the plexus through a communicating branch (*Fig.* 558). At about the level of the superior border of the duodenum communicating veins were noted on occasions to pass between the plexus and one or more of the pancreaticoduodenal veins. It is of interest that in no

specimen were any direct communications observed between the plexus and the trunk or right and left branches of the portal vein. It was not possible, of course, to demonstrate the direction of blood-flow in the veins of the plexus. It seems likely, however, that above the level of the junction of the cystic and common hepatic ducts this is cephalad since the veins pass directly into the liver parenchyma; below this level the communications of the plexus with the pancreaticoduodenal veins would appear to indicate that the direction of the blood-flow is caudad into these larger veins to reach the liver via the superior mesenteric and portal route.



A B

FIG. 557.—A, Petren's paracholedochal veins are present and well shown in this specimen; that on the right comes into view at the angle of junction of the cystic and common hepatic ducts and proceeds cephalad to cross the right hepatic duct anteriorly and enter the liver parenchyma; the left vein is visible from above the duodenum, where it branches, to about the midpoint of the common hepatic duct, where it disappeared behind the margin of the duct and could not be traced further —the inferior branched portion of this vein joined with others to form a plexus (paracholedochal) as noted by Grant (*see* text). Both these veins communicate at intervals along their course with those of the epicholedochal plexus which is seen outlined on the common bile-duct and common and right and left hepatic ducts, the veins of the plexus on the last two ducts entering the liver parenchyma. The inferior cystic vein terminates in the right vein of Petren. Absence of plexus on the cystic duct. B, Key line-drawing.



A B

FIG. 558.—A, In this specimen the cystic duct and supraduodenal portion of the common bile-duct are seen, but almost the entire common hepatic duct is obscured by the overlying quadrate lobe of the liver. The epicholedochal venous plexus is shown very clearly on both the common bile-duct and the small, visible part of the common hepatic duct. The junction of the cystic and common hepatic ducts is poorly defined because of the fatty tissue present in this region. The inferior cystic vein courses above and parallel to the cystic duct and is seen to bifurcate, the upper branch proceeding medially, possibly to terminate in the epicholedochal plexus on the common hepatic duct; the lower branch passes caudad in front of the terminal part of the cystic duct and disappears behind the right border of the common bile-duct. A communicating vein is seen to pass between this lower branch and the epicholedochal plexus. Again the absence of the plexus on the cystic duct is to be noted. B, Key line-drawing.

One aspect of the plexus that remains to be considered is that of its extramural relationship to the common duct. I have stated previously that the plexus is not just close to this duct but actually lies in intimate contact with its wall. It seemed to me that my injection studies should be able to furnish confirmatory evidence of the validity of this clinical observation. Therefore, with this objective in mind, from time to time while these studies were in progress portions of common ducts, using only those on which the veins of the epicholedochal plexus had already been outlined by the injected gentian violet, were taken for transverse section. When paraffin sections were made it was found repeatedly that none of the gentian violet was present in them, this apparently being due to the solvent action on the dye of one or more of the solutions used in the preparation of these sections. Small, thin-walled vessels were always noted lying on the outer coat of the duct wall, but, in the absence of the gentian violet in their lumina or of the staining of their walls with the dye, these vessels could not be positively differentiated from those of the lymphatic system. Dr. D. R. Dickson, Associate in the Department of Pathology, accordingly suggested trying instead the frozen-section technique by which contact of the dye with any solution would be avoided. *Figs.* 561, 562 exemplify the success achieved by the practical application of his suggestion. In these illustrations are seen vessels each with its wall stained with gentian violet (and in consequence standing out in marked contrast to the remaining unstained tissues), proving conclusively that they are veins. These veins, however, are seen to be lying on the outer coat of the duct wall and in intimate contact with it—that is, they are epicholedochal. These transverse sections, then, show the presence of epicholedochal veins, but the fact that they were seen outlined as the epicholedochal plexus on the wall of the intact duct before the sections were cut indicates that these veins are elements of this plexus. Thus these studies furnish evidence which confirms the validity of the clinical observation that the plexus is in intimate contact with the wall of the common duct and at the same time provides justifiable grounds for the suggestion, made earlier, that the term 'epicholedochal venous plexus' be considered an appropriate designation for it. Further, these sections show that the intimate relationship existing between the veins of the plexus and the duct wall is

augmented by their actual attachment to it with connective tissue, this explaining why trauma that would tend to separate a vein of the plexus from the duct wall is likely to result instead in the tearing of the thin wall of the vein.

Particularly to be noted is the consistent failure of these injection studies to demonstrate the presence of a venous plexus on the cystic duct. This substantiates the clinical observation mentioned earlier and emphasized as an important factor in the differentiation between the cystic and common ducts during operations on the extrahepatic biliary tract.

FIG. 559.—Line-drawing of a specimen showing the epicholedochal venous plexus well delineated with the dye on the right, left, and common hepatic ducts. The veins of the plexus on the right and left hepatic ducts are seen entering the liver parenchyma. There is present an unusual termination of the inferior cystic vein, which trifurcates to end in the plexus, two of the branches joining it on the anterior surface of the common hepatic duct and the third doing so on its posterior surface. No veins of Petren were present in this specimen. Absence of plexus on the cystic duct. The outcome of this promising specimen was very disappointing, for at the stage of dissection shown here extravasation of the dye occurred over the common bile-duct and spread quickly to involve nearly the whole specimen, rendering it useless for photography or further drawing.

In addition to having served the purpose of demonstrating the presence and characteristics of the epicholedochal venous plexus, these injection studies furnished certain other anatomical information recorded and discussed below.

The course and termination of the inferior cystic vein were seen to be subject to many variations. Briefly, those encountered were as follows: (1) The vein turned cephalad, running on the right of the common hepatic duct and parallel to it to cross in front of, or behind, the right hepatic duct, and terminated by entering the liver parenchyma at the porta hepatis. (2) It terminated in the right long vein of Petren. (3) It divided (as mentioned above) into two or more branches, these ending in the epicholedochal plexus on either the anterior or posterior aspects of the common duct or on both. (4) It pursued a course to the left and somewhat caudad, crossing in front of the common hepatic duct to end in the left gastric vein. (5) Its course was caudad and slightly to the left in front of the common bile-duct, terminating in a vein of the pancreaticoduodenal complex just behind the superior border of the duodenum.

Such findings as these are of interest in view of the teaching of Sappey, accepted by generations of anatomists and still recorded without question or comment in some text-books of anatomy, that this vein empties into the right branch of the portal vein. Indeed, there are those whose investigations have shown this termination of the vein to be the exception rather than the rule. Petren, for example, found in 50 specimens only 1 in which this vein emptied into the right branch of the portal vein and another where it ran directly into the portal trunk. In other words, in 49 out of 50 cases the vein terminated in some way other than that described by Sappey. Douglas, Baggenstoss, and Hollinshead (1950), investigating the anatomy of the portal vein and its tributaries, found that in only 12 of 92 specimens examined was there evidence to suggest possible termination of the cystic vein in the proximal segment of the portal vein. No mention is made of the right branch of the portal vein in this connexion. These authors remark that variations were encountered so frequently that "in the case of certain veins of the portal system it appears quite impossible to propound a 'normal' configuration. Anomalous patterns, therefore, must be considered only those which occur somewhat less frequently than others". During my injection studies I never observed the inferior cystic vein to drain directly into either the trunk or the right branch of the portal vein.

A B

FIG. 560.—A, This is the only specimen from a case of portal cirrhosis—note portion of 'hobnail' liver, upper right. A long paracholedochal vein of Petren, of somewhat increased calibre, is seen crossing the common bile-duct anteriorly and then proceeding cephalad along the left border of the common hepatic duct. This vein communicates with the epicholedochal plexus (seen outlined to a moderate extent) at several points along its course. It is to be noted that, in contrast to the enlargement of the long vein, the veins of the plexus show no increase in diameter; this indicates that even if the enlargement of the long vein were the result of portal obstruction, rather than being coincidental, then in this particular case such obstruction did not have a demonstrably similar effect upon the veins of the epicholedochal plexus. B, Key line-drawing.

In view of the considerations given previously to the possibility of the effect of certain pathological conditions upon the veins of the epicholedochal plexus, *Fig.* 560 possesses an uncommon interest in that it shows the specimen from the only case of Laennec's cirrhosis encountered during the injection studies and, as such, I feel it calls for special comment. Two features in particular are to be noted, namely, a vein of Petren of somewhat larger calibre than that usually observed and an epicholedochal plexus which shows no abnormality in the size of its veins. One

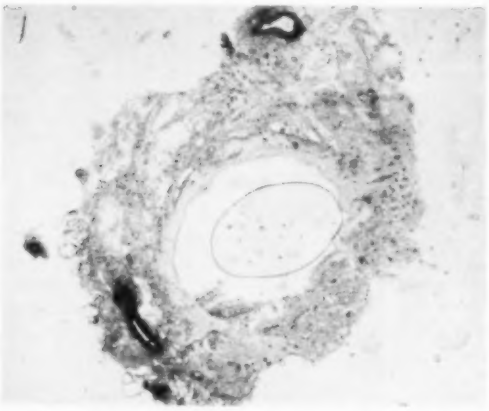


FIG. 561.—Photomicrograph (× 15), in black-and-white, of an unstained transverse section through the common duct of an injected specimen using the frozen-section technique. The wall of the duct is thicker than usual in proportion to the diameter of the lumen (cf. *Fig.* 562, where a more normal relationship is shown) and the outer coat appears somewhat disrupted on the left side of the section, making its outer limit difficult to discern in this region. Two small vessels are seen with their walls stained with the gentian violet, proving that they are veins and not lymphatics; they lie in intimate contact with the outer coat of the duct and are thus epicholedochal in location. These two features exhibited by the vessels indicate that they belong to the epicholedochal plexus, as this was already seen outlined with the dye on the wall of the intact duct before the section was cut. Note that the veins are seen to be actually attached to the duct wall by connective tissue, this explaining why trauma tending to separate them from the duct usually results instead in the tearing of their thin walls.

consistent finding in this type of cirrhosis, consequent upon the obstruction of the portal system by the hepatic fibrosis, is a dilatation of varying degree of the veins of this system. While in this case the dilatation of the vein of Petren might be coincidental, yet it could possibly represent a pathological change due to the portal obstruction present; if one is prepared to accept this latter explanation then the lack of dilatation of the veins of the epicholedochal plexus assumes a greater interest and importance since it signifies that in this case at least of portal cirrhosis the intrahepatic obstruction present was insufficient to cause dilatation of the veins of the plexus in spite of the fact that the condition was well advanced, as indicated by the marked 'hobnail' appearance of the liver. The question as to whether or not the portal obstruction in cirrhosis can result in dilatation of the veins of this plexus leads me to refer to an article by Shapiro and Robillard (1948). Although these authors wrote primarily concerning the arterial blood-supply of the common and hepatic bile-ducts, they devoted their last paragraph to a consideration of the veins of the extrahepatic bile passages. Here they quote Petren as stating that the veins of the extrahepatic bile-passages, having ascended into the liver, then enter into the radicles of the hepatic veins directly without major anastomoses between the portal and hepatic venous systems, and that for this reason Petren claimed that there is no dilatation of the veins along the common duct in

FIG. 562.—This transverse section of the common duct (× 12·5) was the best of the frozen sections of injected specimens examined, and consequently the decision was made to include it among the illustrations in spite of the fact that microphotography yielded a most disappointing result. The pencil drawing above, therefore, was done in an attempt to convey, though necessarily in limited measure, the outstanding merit of the original slide. In it are seen three thin-walled vessels exhibiting the same characteristics (but shown much more clearly) as those displayed by the two vessels in *Fig.* 561—namely, their walls are stained with the gentian violet, they lie in intimate contact with the outer coat of the duct wall, and they are attached to it by connective tissue—in other words, they, too, are veins of the epicholedochal plexus. Two tiny thin-walled arteries are also seen, each in close proximity to one of the veins.

cirrhosis of the liver. Anyone who has studied Petren's paper will be more than surprised to read these quotations for the following reasons: The only statement Petren makes in regard to the intrahepatic course of the veins of the extrahepatic bile-passages is that these veins, having penetrated into the liver, quickly ramify into capillaries; the concept, instead, that they enter the hepatic vein radicles directly, as quoted by Shapiro and Robillard, is not mentioned at all in Petren's article. Further, since the word 'cirrhosis' does not even appear in Petren's paper it is perhaps superfluous to point out that any claim by him relating this condition to the state of the veins of the extrahepatic bile-passages is likewise not to be found in the text of his article.

From time to time during my injection studies glimpses were caught of the proximal part of the retroduodenal portion of the common bile-duct. These indicated, as one would anticipate, that the epicholedochal venous plexus is apparently present also on the wall of this portion of the duct. Unfortunately, its extent or characteristics here could not be determined by these studies because any

attempts to carry out the necessary dissections would certainly have resulted in the tearing of one or more of the large veins which abound in this region, with consequent obliteration of the plexus by the extravasated dye. However, I feel sure that these aspects of the plexus as it lies on the wall of this portion of the common bile-duct could be demonstrated satisfactorily by studies similar to those recorded herein but employing, instead of the dye, a medium which solidifies after injection. Moreover, the use of such a medium should serve additionally not only to verify the characteristics of that portion of the plexus investigated here but might well also reveal details of its anatomy undiscovered in these reported studies because of the limitations imposed by the employment of a medium which remained fluid after injection.

SUMMARY

1. A venous plexus observed on the wall of the supraduodenal portion of the common duct is described and illustrated.

2. The term 'epicholedochal venous plexus' is suggested as an appropriate designation for it.

3. The recognition of this plexus and its utilization as a means of early and positive identification of the common duct during operations on the extrahepatic biliary tract are emphasized as being likely to prove of material help in reducing the risk of operative injury to this important duct.

4. Attention is drawn to the absence of a venous plexus on the wall of the cystic duct, and this fact is emphasized as an important aid in differentiating the cystic from the common duct at operation.

5. Injection studies, employing gentian violet as a medium, were undertaken and are described.

6. These studies: (*a*) Confirmed the existence of the epicholedochal venous plexus; (*b*) Verified that the characteristics of this plexus are those observed clinically and described and illustrated in this communication; (*c*) Showed that the plexus is continued on both the right and left hepatic ducts to the porta hepatis; (*d*) Indicated that the plexus is an anatomical entity; (*e*) Failed to demonstrate the presence of a venous plexus on the wall of the cystic duct; and (*f*) Furnished certain other anatomical information which is presented and discussed.

Acknowledgements.—I wish to express my gratitude to Dr. E. L. Benjamin, Head of the Cottage Hospital Department of Pathology, who made possible for me the opportunity to undertake the injection studies reported above by giving me his cordial permission to work in his Department. To Dr. D. R. Dickson, his Associate, who gave so freely of his time as well as assuming the additional burden of photographing many injected specimens, I am deeply indebted; without his help and unfailing co-operation it would have been impossible for me to have completed these studies. To Professor J. C. B. Grant, of Toronto, I am grateful not only for his continued and stimulating interest in my studies while they were in progress, but also for his encouragement and helpful suggestions. My brother, Professor C. F. M. Saint, of Cape Town, I can never thank enough for his invaluable guidance as my mentor from the time of inception of this paper to its completion.

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AZOTÆMIC RENAL OSTEODYSTROPHY

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THE term 'renal osteodystrophy' was introduced by Liu and Chu (1943) to describe the various skeletal complications of chronic renal failure. Fraser and King (1957) and Davis (1958) have included within this definition the bone diseases associated with a primary renal tubular defect (de Toni-Fanconi syndrome, familial vitamin-D-refractory rickets) and also the bone changes associated with severe secondary renal damage in primary hyperparathyroidism. For this reason the authors favour the term 'azotæmic renal osteodystrophy' employed by Stanbury (1957) and Sørensen (1958) to distinguish the skeletal complications associated with chronic renal failure. Azotæmic renal osteodystrophy has been found in association with the following pathological conditions:—

1. Renal hypogenesis.
2. Congenital polycystic kidney.
3. Obstructions in the urinary tract:—
   a. Uretero-pelvic (bilateral).
   b. Uretero-vesical (bilateral).
   c. Enlarged median bar.
   d. Urethral valve.
   e. Neuromuscular inco-ordination of the bladder neck.
4. Chronic pyelonephritis (bilateral).
5. Chronic glomerulonephritis.

Cases of azotæmic renal osteodystrophy attributed to congenital changes at the bladder neck and urethra and to chronic pyelonephritis in association with renal hypogenesis are described. The early diagnosis of such cases is often difficult, and attention

is called to the importance of renal function studies in cases of non-specific anæmia and of rickets in children and adolescents.

CASE REPORTS

Case 1.—This male patient was born in 1934 and, apart from persistent enuresis, development was normal up to the age of 13 years, when he stopped growing. At the age of 14 years he was treated for anæmia and an

FIG. 563.—*Case* 1. Personal appearance. There is slight bilateral genu valgum.

infection of the urinary tract, and examination at that time, carried out elsewhere, revealed the presence of a moderate proteinuria with gross impairment of renal function (urea clearance 18 per cent of average normal); an intravenous pyelogram was unsatisfactory owing to insufficient concentration of the dye; the serum-calcium, inorganic phosphate, and alkaline phosphatase were found to be normal. The lack of development was attributed to chronic nephritis.

He was admitted to this hospital in August, 1954, complaining of pains in the back and weakness of both legs during the past two years. He had a pale, sallow complexion and his height was 4 ft. 9½ in. (*Fig.* 563). A mid-stream specimen of urine showed scanty pus cells and yielded a growth of *B. proteus*. The urea clearance was 13 per cent of average normal and the blood-urea was 124 mg. per cent (*Fig.* 564). There was marked acidosis and hyperchloræmia (CO_2-combining power 15·3 mEq./l., chloride 111 mEq./l.), and a low serum-calcium level (7·8 mg. per cent), but the albumin-globulin ratio was normal (albumin 5·0 mg. per cent, globulin 2·0 mg. per cent). The serum alkaline phosphatase and inorganic phosphate levels were raised (50 King-Armstrong units and 5·0 mg. per cent respectively), but the potassium level was normal (4·5 mEq./l.). The urinary excretion of calcium averaged 50 mg. per 24 hours and the 17-ketosteroids 7·3–11·0 mg. per 24 hours; both the values for the calcium and the ketosteroids are rather low for a man of this age. There was evidence of moderate anæmia (hæmoglobin 75 per cent, red-cell count 4 million per cu.mm.). A radiograph of the long bones and hands (*Figs.* 565, 566) indicated the presence of rickets. The presence of a mild degree of secondary hyperparathyroidism was suggested by the slight erosion of the radial aspect of the carpal phalanges. There was no evidence of renal calcification.

Ascending pyelograms revealed very large bilateral hydronephroses and hydro-ureters, but the bladder showed no cystoscopic abnormality except a moderate grade of trabeculation and some hypertrophy of the internal sphincter (*Fig.* 567). Residual urine in the bladder was 16 oz. A testicular biopsy showed normal

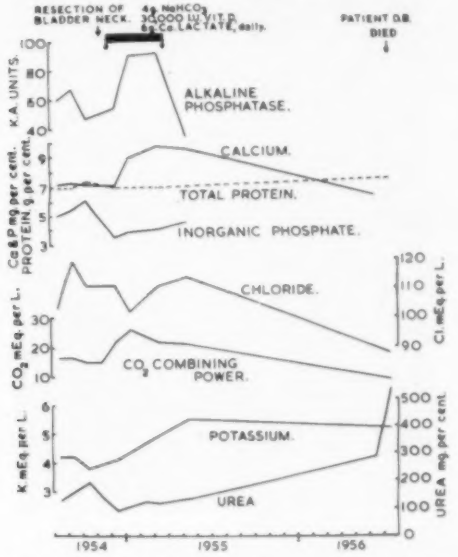


FIG. 564.—*Case* 1. The effect of vitamin D and alkali therapy on the blood chemistry.

spermatogenesis. A calcium, phosphorus, and nitrogen balance was carried out on a moderately low intake of calcium (350 mg. per day). The patient was found to be in slight negative balance with respect to calcium and the ratio of urinary to fæcal calcium was much lower than normal, the average urinary calcium being 15 mg. per day (*Fig.* 568). There was a marked retention of phosphorus and nitrogen and the theoretical phosphorus balance agreed well with that obtained experimentally.

By the suprapubic route a large V-shaped resection of the lower part of the bladder neck, which was found to be hypertrophied, was performed in November, 1954. A biopsy of the right tibia near the upper epiphysis showed great irregularity of the epiphysial line, with defective endochondral ossification. Many of the new bony trabeculæ retained a cartilaginous core and islets of cartilage lay deep to the epiphysial line; the bony trabeculæ were separated by vascular connective tissue, the general appearance being indicative of rickets with evidence of osteitis fibrosa (*Fig.* 569 A). The resection of the bladder neck resulted in much better emptying of the bladder and the residual urine was reduced to 3 oz. The provision of better urinary drainage, and treatment with sodium bicarbonate (4 g.), calcium lactate (6 g.), and vitamin D (30,000 I.U.) daily, resulted in some improvement in the blood chemistry, the urea level falling from 193 to 90 mg. per cent and the CO_2-combining power rising from 15 to 24 mEq./l. in fourteen days (*Fig.* 564). The patient continued, with some lapses, on this régime until his death. A radiograph of the wrists and knees

four months later showed that there had been marked recalcification in the lower end of the radius, the epiphysial line now being clearly defined, the rickety changes having in fact resolved. For more than eighteen months the boy was reasonably well and was able to work.

In June, 1956, he was admitted to hospital with skin eruptions of the arms and legs; a biopsy of one of the lesions of the legs showed a non-specific keratinizing papillomatous lesion with pigmentation of the basal epithelial cells and some acanthosis; no definite cause was found for these eruptions. The blood-urea had now risen to 288 mg. per cent, the albumin-globulin ratio was 1·3 (albumin 4·2 mg. per cent, globulin 3·3 mg. per cent), and the serum-calcium had fallen to 6·4 mg. per cent. The residual urine had now increased to 8 oz. One month later he was readmitted complaining of weakness, loss of appetite, and blurring of vision, and was in fact virtually moribund. The blood-urea was now 430 mg. per cent and the CO_2-combining power 9·1 mEq./l. His condition deteriorated rapidly and he died four days after admission. There was no evidence of tetany at any time.

At autopsy the bladder was large, thin-walled, and trabeculated. There were gross bilateral hydronephroses and hydro-ureters, both kidneys containing thick, green pus giving a growth of *Ps. pyocyanea* on culture; the

FIG. 565.—*Case* 1. Radiograph of the upper end of the femur showing Looser's zone on the undersurface of the femoral neck.

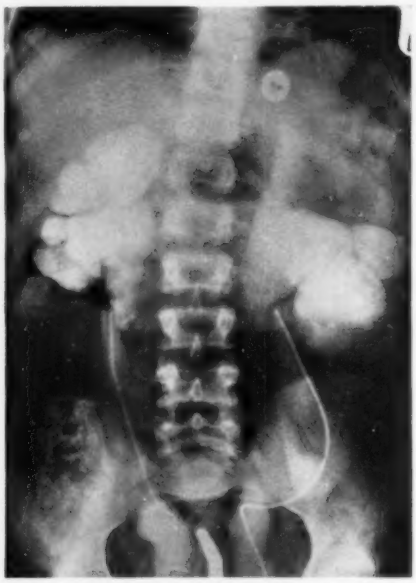


FIG. 567.—*Case* 1. Ascending pyelogram showing severe bilateral hydronephrosis. There is also very marked dilatation of the lower ends of both ureters.

A B C

FIG. 566.—*Case* 1. A (Dec. 13, 1954), Radiograph of the lower ends of the right radius and ulna showing rickety epiphyses (before treatment). B (May 5, 1955), Radiograph showing marked improvement after treatment with vitamin D and calcium. C (Jan. 11, 1956), Radiograph showing still further improvement in the epiphyses with continued treatment.

renal substance on both sides was reduced to the merest shell. In the urethra 4 cm. from the bladder neck was a diverticulum 2 cm. in diameter with a well-developed free, crescentic anterior margin which may have acted as a flap valve causing partial secondary obstruction to the voiding of urine. Two small superior and two larger inferior parathyroid glands were found, the total weight being 480 mg. The bones appeared to be normal on gross examination and there were no skeletal deformities. The testes were small and firm.

Histologically the diverticulum was lined by transitional epithelium showing large areas of squamous metaplasia. The hydronephrotic kidneys showed typical chronic pyelonephritis in the small amount of kidney tissue remaining, though there was virtually complete obliteration of all functioning renal tissue. The parathyroid glands were composed of compact masses of small 'chief cells' with minimal fat and some foci of oxyphil cells. There was no evidence of metastatic calcification in the kidneys, lungs, or stomach, though the aorta and many medium-sized arteries showed calcified atheromatous plaques. In the bones the calcified lamellæ were surrounded by broad, irregular zones of homogeneous osteoid and the marrow spaces contained poorly arranged trabeculæ of uncalcified osteoid with abundant surrounding vascular connective tissue; in many areas the changes were slight, but in some places they were prominent, the osteoid material and the adjacent connective tissue occasionally forming a complicated pattern though the general appearances were those of osteomalacia (adult rachitic osteodystrophy). In the jaw, the ribs, the neck of the femur, and the upper end of the tibia were prominent foci of lacunar reabsorption with accumulation of osteoclasts typical of osteitis fibrosa (*Fig.* 569 B). The testes showed virtual absence of spermatogenesis, with some thickening of the lamina propria of the seminiferous tubules and prominence of the interstitial cells. Pigmentation of the skin is well known in chronic renal failure (e.g., Claireaux, 1953), and a quite marked basal-cell pigmentation was observed in this case.

It is concluded from the autopsy and other findings that the initial defect in this patient was an obstruction in the urinary tract primarily at the bladder neck, with a secondary obstruction associated with a congenital diverticulum of the urethra; these lesions led to fatal chronic renal failure and renal osteodystrophy; the bony skeleton showed the changes both of osteomalacia and secondary hyperparathyroidism.

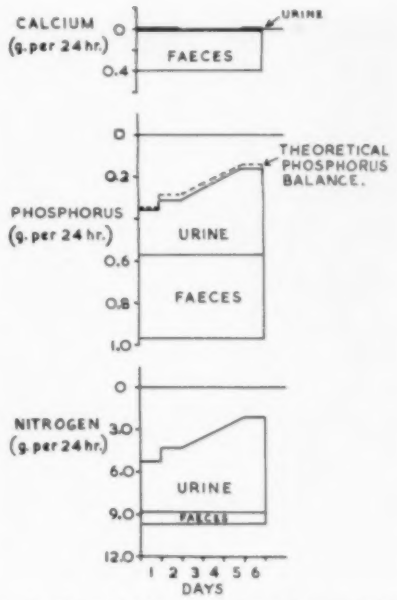
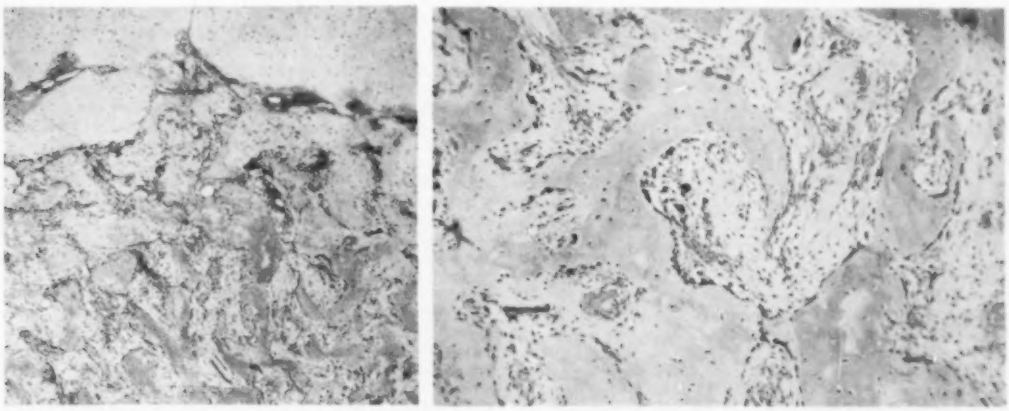


FIG. 568.—*Case* 1. Calcium, phosphorus, and nitrogen balance.



A B

FIG. 569.—*Case* 1. A, Tibial biopsy. There is great irregularity of the epiphysial line. Endochondral ossification is defective and many of the new bony trabeculæ still have a cartilaginous core and a few islands of cartilage lie deep to the epiphysial line. The bony trabeculæ are separated by vascular connective tissue with abundant osteoclasts. The changes are those of renal rickets with evidence of hyperparathyroidism. H. and E. (× 21.) B, Rib—post-mortem. There is abundant fibrovascular connective tissue with osteoclasts between the bony trabeculæ, which are very poorly calcified. The appearances are those of hyperparathyroidism, but the presence of osteoid plaques is evidence of renal rickets. H. and E. (× 150.)

Case 2.—This was a boy aged 13 years, with no previous history of note except persistent thirst and occasional attacks of central abdominal discomfort unaccompanied by vomiting; he had a fracture of the right ankle when aged 11 years (June, 1957). A radiograph of

the right ankle in June, 1959, was reported as showing the typical appearance of rickets. The blood-urea then was 210 mg. per cent, serum-calcium 9·7 mg. per cent, serum-phosphate 5·8 mg. per cent, and alkaline phosphatase 59 King-Armstrong units. The urine contained some heat-coagulable protein, but no other abnormality was observed. An intravenous pyelogram showed no excretion by either kidney. On a low-protein, high-carbohydrate diet his blood-urea fell to 74 mg. per cent.

The patient was admitted to this hospital in July, 1959, for further examination. He had a pale, sallow complexion but was mentally and physically active and co-operative. His appetite was good and there were no symptoms referable to the urinary tract. A systolic murmur was noted in the pulmonary area. Several midstream specimens of urine were examined, but these revealed only scanty red cells with no leucocytes or casts and yielded no growth on culture. There was an appreciable proteinuria and the urine output averaged 2 litres per day. The blood-urea was 330 mg. per cent, CO_2-combining power 24 mEq./l., serum-calcium 10·0 mg. per cent, serum-phosphate 5·4 mg. per cent, and hæmoglobin 50 per cent. No excretion was observed on an intravenous pyelogram, the renal shadows being reduced in size. No abnormality was found on cystoscopy except a slight dilatation of the posterior urethra. A cystourethrogram revealed some sacculation of the bladder and no abnormality was seen on the ascending urethrogram; there was no evidence of a urethral valve during micturition, and the only unusual feature was a little backward angulation of the urethra just above the verumontanum, but this did not appear to cause any significant obstruction and the stream of urine appeared to be satisfactory. An open biopsy of the right kidney was performed; the organ was somewhat hydronephrotic and its surface was irregularly scarred. Histologically the biopsy specimen showed a combination of hydronephrotic parenchymal thinning with extensive interstitial fibrosis, accompanied by chronic inflammatory cell infiltration, tubular atrophy, and gross focal thickening of small arteries; there was a moderate degree of glomerular hyalinization and areas of tubular dilatation were noted, these tubules being lined by low columnar epithelium. The mucosa lining the deep surface appeared normal and there was no evidence of infection. No calcification was seen. The appearances were those of hydronephrosis with associated chronic pyelonephritis.

Radiography of the wrists and ankles showed some expansion of the lower ends of the tibiæ with increase in width of the epiphysial plate with irregularity of rickety type. Erosion of the lower ends of the shafts of both radii was noted and all the bones appeared osteoporotic. There were well-marked changes of secondary hyperparathyroidism at the inner aspect of the upper end of the shaft of the tibia and in several of the middle phalanges of the hands (*Figs.* 570–572).

FIG. 570.—*Case* 2. Radiograph of lower ends of tibia and fibula, with rickety changes at the epiphyses.

FIG. 572.—*Case* 2. Radiograph of upper end of right tibia and fibula. There is subperiosteal resorption on the undersurface of the upper end of the tibia due to hyperparathyroidism.

FIG. 571.—*Case* 2. Radiograph of phalanges showing well-marked subperiosteal resorption of bone in the middle phalanges due to secondary hyperparathyroidism.

A diagnosis of osteodystrophy due to renal failure from chronic pyelonephritis was made. Treatment with sodium bicarbonate (8 g.), potassium citrate (3 g.), calcium lactate (3 g.), and vitamin D (3600 I.U. in halibut oil) daily was started in August, 1959, and he was discharged home on this régime.

The patient was readmitted to hospital for further investigations in January, 1960. He had no complaints

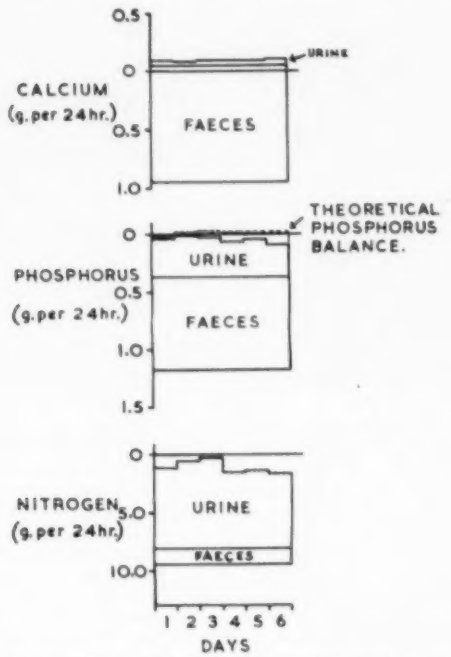


FIG. 573.—*Case* 2. Calcium, phosphorus, and nitrogen balance.

except for tiredness and occasional loss of appetite. The blood-urea level had fallen slightly to 264 mg. per cent, but the serum-potassium and serum-phosphate levels were moderately elevated (5·9 mEq./l. and 7·0 mg. per cent respectively). The remainder of the blood chemistry was as follows: sodium 137 mEq./l., choride 93 mEq./l., CO_2-combining power 30·0 mEq./l., alkaline phosphatase 35 King-Armstrong units, calcium 9·5 mg. per cent, total protein 7·0 g. per cent, and hæmoglobin 40 per cent. One pint of packed cells was given intravenously, resulting in a rise in the blood hæmoglobin level to 67 per cent. The urea, creatinine, and phosphate clearances indicated a gross impairment of renal function: urea clearance 11 per cent (corrected for size); creatinine clearance 8·0 ml. per min.; phosphate clearance 5·4 ml. per min. A 6-day calcium, phosphorus, and nitrogen balance on a daily intake of 1 g. of calcium and 10 g. of nitrogen showed that the patient was in moderate negative calcium balance (*Fig.* 573); there was some retention of phosphorus and nitrogen and the fæcal excretion of calcium and phosphorus was considerably higher than normal. All medication was stopped during the period of the balance test and this resulted in a gradual deterioration in his condition, with some loss of appetite on the final day of the balance. Sodium bicarbonate (12 g. daily) resulted in a dramatic improvement in the patient's condition within two days. A radiograph of the epiphyses revealed rachitic changes more marked than those seen in July and September, 1959.

The patient was discharged home in January, 1960, on the following régime: sodium bicarbonate (9 g.), calcium lactate (3 g.), and calciferol (50,000 I.U.) daily. His blood chemistry at this time was as follows: sodium 135 mEq./l., CO_2-combining power 27·0 mEq./l., urea 231 mg. per cent, calcium 8·5 mg. per cent, phosphate 6·3 mg. per cent, protein 6·9 g. per cent, and magnesium 1·8 mg. per cent. A radiograph in April, 1960, showed no

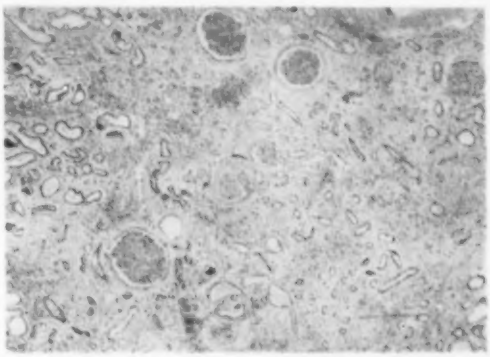


FIG. 574.—*Case* 2. Kidney. There is marked interstitial fibrosis and a reduction in the number of glomeruli, although there is also some glomerular hyalinization. A few small, dense foci of tubular calcification are seen. H. and E. (× 17·5.)

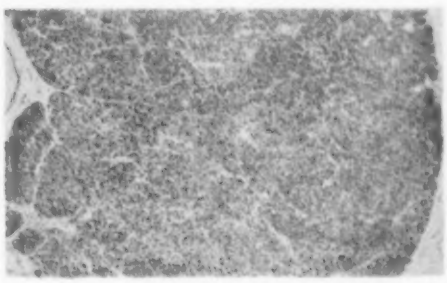
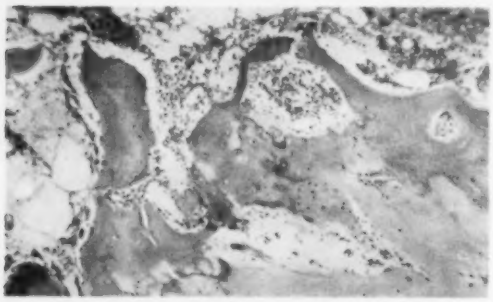


FIG. 575.—*Case* 2. Parathyroid, post-mortem. There is well-marked hyperplasia. H. and E. (× 17·5.)

improvement in the rickety epiphyses. The boy was readmitted to hospital on June 21, 1960, by which time he was gravely ill, and shortly afterwards he developed uræmic fits. The blood-picture was as follows: plasma-urea 357 mg. per cent, serum-sodium 139 mEq./l., serum-potassium 6·4 mEq./l., serum-chloride 85 mEq./l., and CO_2-combining power 24 mEq./l. Hæmodialysis was carried out on the next day with considerable improvement in the blood-picture, which was now as follows: plasma-urea 72 mg. per cent, serum-sodium 145 mEq./l., serum-potassium 3·7 mEq./l., serum-chloride 105 mEq./l., serum CO_2-combining power 32 mEq./l. Within a week of the hæmodialysis the blood-picture had deteriorated, the figures on June 29 being: plasma-urea 345 mg. per cent, serum-sodium 127 mEq./l., serum-potassium 5·7 mEq./l., serum-chloride 87 mEq./l., serum CO_2-combining power 24 mEq./l. The patient died on July 3.

At autopsy both kidneys were very small, the right weighing 29 g. and the left 34 g. The renal pelvis and the calices were dilated, the cortex showing typical pyelonephritic scars. Histologically the kidneys showed much featureless connective tissue which did not contain recognizable renal elements nor any marked inflammatory cell infiltration. There were a few enlarged, cellular, hypertrophied glomeruli associated with dilated

tubules surrounded by abundant fibrous tissue; the intrarenal vessels showed well-marked hypertensive changes. The appearances were those of renal fibrosis with superadded hydronephrosis and chronic pyelonephritis (*Fig.* 574). It was difficult to be certain whether the renal fibrosis was the result of long-standing hydronephrosis and infection, or whether it was the result of primary renal hypoplasia; the latter, on balance, seemed to be more likely. The bladder showed chronic inflammatory changes, with some hypertrophy of the detrusor muscle. Three enlarged parathyroid glands were found measuring respectively 1·2, 0·8, and 0·7 cm. in their long axis and weighing respectively 373, 286, and 247 mg.



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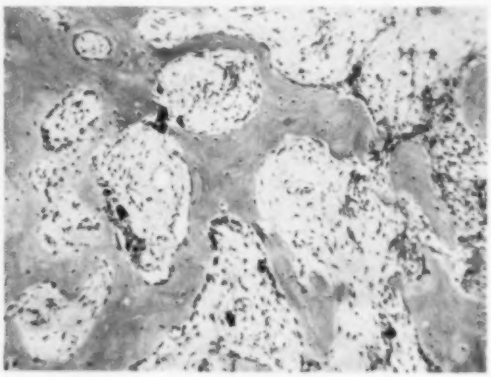

B

FIG. 576.—*Case* 2. A, Rib—post-mortem (undecalcified). There are irregular osteoid seams and tracts of uncalcified osteoid indicating renal rickets. H. and E. (× 125.) B, Rib—post-mortem (undecalcified). There is osteoclastic erosion of the trabeculæ, indicating secondary hyperparathyroidism. H. and E. (× 135.)

each (*Fig.* 575). Histologically the glands were composed of compact masses of water-clear and chief cells, supported by dense fibrous trabeculæ; there were some scanty foci of oxyphil cells but no fatty infiltration. Histology of the long bones (*Fig.* 576) showed well-marked lacunar resorption with numerous small foci of osteoclasts, while broad osteoid seams were present without calcification.

This is an example of chronic renal failure and renal osteodystrophy, the bones showing both rickets and secondary hyperparathyroidism, with the microscopical changes resulting from both causes being more advanced than in *Case* 1.

DISCUSSION

Obstruction of the lower urinary tract in young males is most commonly due to obstruction at the bladder neck or to the presence of a valve in the posterior urethra. Only very rarely has a diverticulum of the urethra been noted as a primary or secondary cause of obstruction. Urethral diverticula are uncommon and may be either congenital or acquired as a result of trauma, infection, or obstruction distal to the diverticulum. In *Case* 1 the primary cause of the obstruction in the lower urinary tract was a muscular hypertrophy of the bladder neck, but at autopsy a urethral diverticulum, undiagnosed in life, was found as a secondary cause of obstruction. The diverticulum was presumed to be congenital as none of the above factors was known to be operative and the pouch was lined by intact epithelium with a well-marked lamina propria and underlying smooth muscle. It has been suggested by Johnson (1923) that congenital urethral diverticula might arise from the failure of the cloacal fossa to fuse in the ventral midline and to form the floor of the urethra.

Urethral diverticula are liable to recurrent infection and to urinary stagnation, which may lead to calculus formation. Very rarely a diverticulum may produce partial or severe obstruction in the lower urinary tract, either by compression of the urethra when it is distended with urine during micturition, or by the presence of a flap-like roof which may act as a urethral valve; the latter was considered to be the manner in which the secondary obstruction was produced in *Case* 1. Gross and Bill (1948) reported 3 cases of urinary obstruction in male children due in each case to a 'concealed diverticulum' of the urethra, the title of the paper indicating the difficulty that exists in the diagnosis of the condition. In the first two children, aged 5 and 2 years respectively, the abnormality was unrecognized before death and resulted in infection of the urinary tract and uræmia; in the third child, aged 9 months, the diverticulum was successfully diagnosed and the obstruction removed by surgical obliteration of the flap-valve. In none of these cases was there any external evidence of a diverticulum, and the authors recommend urethrography as the best method of establishing a correct diagnosis. Mills (1955) reported 2 cases of chronic retention of urine in boys caused by diverticula in the anterior urethra, both of which were diagnosed by urethrography. The early removal of any obstruction in the urinary tract is essential if renal impairment and subsequent osteodystrophy are to be treated successfully or even prevented. In infancy, when the bone changes are minimal, the removal of an obstruction may preserve the surviving renal parenchyma, and calcification of the bones should proceed normally. Treatment with vitamin D and alkalis is most likely to produce a good response in re-calcification of bone if it is instituted before puberty (Howard, 1938; Claireaux, 1953).

In the second case the renal failure appeared to be due to primary renal hypoplasia with secondary pyelonephritis. Though the amount of surviving renal tissue was greater in *Case* 2 than in *Case* 1, the skeletal changes were histologically more advanced.

Stanbury (1957) observed that the only biochemical abnormality that is constantly associated with renal osteodystrophy is elevation of the blood

level of the non-protein nitrogen. A metabolic acidosis is usually, but not always, present, and this generally responds well to alkali therapy, as occurred in the present cases. The serum-calcium level is frequently depressed, sometimes to very low levels, and this is generally attributed to the presence of an elevated phosphate level, although this does not appear to be an adequate explanation in many cases. The usual signs of hypocalcæmia (tetany and positive Chvostek's or Trousseau's sign) may not be encountered, however, and the reason is not clear.

Impairment of renal function may give rise to a variety of changes in the skeleton and there is no single microscopical picture of renal osteodystrophy. Crawford, Dent, Lucas, Martin, and Nassim (1954) pointed out that it is difficult to account for all the bone changes on the basis of current knowledge, but that the two patterns most commonly found are those of rickets (or osteomalacia) and osteitis fibrosa. The nature of the bone lesions in any particular case appears to depend on the extent and duration of the renal disease and on the timing and interplay of the effects of acidosis and secondary hyperparathyroidism (Claireaux, 1953; Prosterman, 1956), and, of course, on the age of the patient. In the present cases the bone changes were predominantly those of rickets, with slight evidence of osteitis fibrosa in *Case* 1 and more marked changes in *Case* 2. Stanbury (1957) observed that it is those cases with only slight evidence of osteitis fibrosa which are most likely to respond favourably to large doses of vitamin D, and this was confirmed by the good response in *Case* 1 and the poor response in *Case* 2. In this respect the rickets (or osteomalacia) of renal failure resembles familial 'vitamin-D-resistant rickets' and it has been suggested that there is an acquired insensitivity to the action of vitamin D in chronic uræmia (Liu and Chu, 1943). These authors considered that insensitivity to vitamin D is an important factor in the genesis of the bone disease, a view which is supported by Stanbury (1957). The reason for the diminished response to vitamin D is not clear, but the mechanism would appear to differ from that of familial 'vitamin-D-resistant rickets' in which resistance has been attributed to a primary renal loss of phosphate (Winters, Graham, Williams, McFalls, and Burnett, 1958). Resistance to vitamin-D therapy does not appear to be due to a failure to absorb the vitamin, since there is also a failure to respond to vitamin D administered intramuscularly (Liu and Chu, 1943).

Balance studies on a low or normal intake of calcium reveal a negative calcium balance (*Figs.* 564, 573). The calcium loss is aggravated by an increased intake of phosphate, but a positive balance can usually be achieved with a high-calcium–low-phosphate intake (Liu and Chu, 1943). The renal excretion of calcium and phosphorus is depressed and there is an increase in the fæcal excretion of these elements (*Figs.* 564, 573). Mitchell (1930) suggested that there is a block in the intestinal absorption of calcium resulting from an increase in the excretion of phosphate into the intestine. This view, which has been supported by Albright, Drake, and Sulkowitch (1937) and Liu and Chu (1943), is not the complete explanation, however, since the serum-phosphate level is within normal limits in some cases.

Yendt, Connor, and Howard (1955) observed that the *in vitro* calcification of rachitic rat cartilage is inhibited in the presence of sera from patients with renal insufficiency; these authors considered that hypermagnesæmia, frequently observed in renal failure, may account for some of this inhibitory effect, but the main inhibitory factor was not determined. The serum-magnesium level was determined in *Case* 2 and was found to be within the normal range. If these findings are applicable to human cartilage and osteoid they would offer a further possible explanation of the reduced anti-rachitic effect of vitamin D in renal osteodystrophy.

The occurrence of metastatic calcification in chronic renal failure has been noted by a number of authors. Mulligan (1947), reviewing 100 cases of metastatic calcification, found that renal disease was present in 23 per cent. No evidence of metastatic calcification was observed in the present cases.

Lack of gonadal development in renal osteodystrophy occurring in early adult life has been noted by Howard (1938) and was observed in *Case* 1; there appears to be no adequate explanation for this finding. Pathological changes have been found occasionally in the pituitary gland in renal osteodystrophy and some authors consider that they account for the dwarfism, infantilism, and polyuria.

Some of the difficulties in the early diagnosis of chronic renal failure are well recognized. In both of the cases described there were no specific indications until puberty, when renal impairment was far advanced. Baird and Lees (1956), describing 3 cases of renal osteodystrophy in adults, emphasized the outstanding symptom of bone pain, but it is doubtful whether this symptom is of value for the early diagnosis of renal failure. Merrill (1955) and Payne (1960) have discussed the early signs of chronic renal failure in some detail and they include anæmia, nocturia, enuresis, easy fatigability, and failure to develop; although these signs are largely non-specific it is suggested that when they are found to be present in a patient, they merit a determination of the blood-urea level and an examination of renal function, unless there are obvious indications to the contrary.

SUMMARY

Two cases of azotæmic renal osteodystrophy are described, one due to an obstruction of the bladder neck and aggravated by a diverticulum of the urethra, the other to chronic pyelonephritis associated with renal hypoplasia. The importance of the early diagnosis of any obstructive uropathy is emphasized. The pathogenesis and treatment of the bone changes occurring in chronic renal failure are discussed.

Acknowledgements.—The authors wish to thank Dr. F. W. Heaton, of the Medical Research Council Unit for Research on Metabolic Disturbances in Surgery, for the magnesium determinations; and the staff of the Metabolic Ward, The General Infirmary at Leeds, for help with the diets and collection of samples.

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A GIANT ADENOMA OF BRONCHUS

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THE usual conception of the size of a bronchial adenoma lies somewhere between a pea and a plum. The adenoma which arises from the main or lobar bronchi conforms to this size, but the one which arises more peripherally may reach much greater dimensions. The case reported is of the peripheral type of leison, and a search of the literature has failed to reveal one of comparable size.

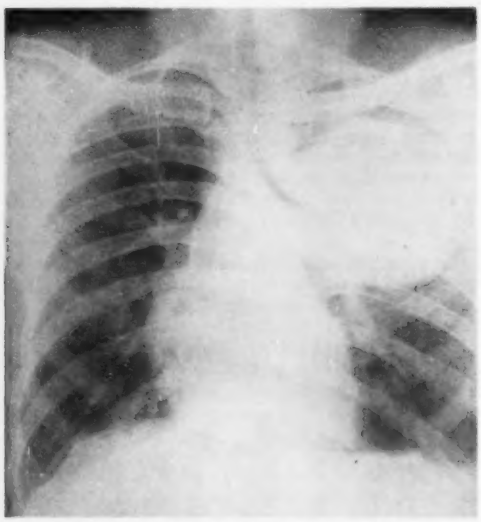


FIG. 577.—Postero-anterior radiograph in 1955.

CASE REPORT

A male Nigerian, aged 33 years, was admitted to University College Hospital, Ibadan, on Jan. 1, 1959. In 1953 his sputum had been blood-stained on one occasion, and in 1954 he had been admitted to a Mission Hospital in Western Nigeria on two occasions, when a diagnosis of left-sided pneumonia had been made. He was re-admitted to the Mission Hospital the following year, on account of pain in the upper part of the left chest. A chest radiograph taken at that time showed a large rounded opacity in the region of the left upper lobe (*Fig.* 577). During the next three years the patient continued to have recurrent attacks of pain associated with a non-productive cough, and increasing dyspnœa. It was as a result of these symptoms that he was admitted to University College Hospital, Ibadan. Physical examination revealed diminished air entry in the left upper zone. There was no clubbing.

RADIOLOGICAL EXAMINATION.—A chest radiograph confirmed the presence of an opacity occupying the upper half of the left hemithorax (*Fig.* 578). On comparing this latter film with the one taken three years previously there had been no obvious increase in size of the lesion. A bronchogram showed distortion of the left upper lobe bronchus and no filling of the apico-posterior segment. No tumour was visible bronchoscopically.

AT OPERATION (Feb. 2, 1959).—A left thoracotomy through the bed of the fifth rib was performed. A tumour, which was softer than a typical carcinoma, was found presenting in the interlobar fissure (*Fig.* 579). There were no enlarged hilar lymph-nodes. The lung tissue on both sides of the fissure was seen to be displaced and compressed, ensheathing the tumour and giving the appearance of a false capsule. It was possible to remove the tumour without resecting pulmonary tissue, as the compressed parts of the upper and lower lobes separated from the tumour surface by a combination of blunt and sharp dissection. The base of the tumour was attached to the wall of the apico-posterior bronchus close to its origin and, following removal, a small defect was seen to be present in the side of the bronchus. This was closed and the whole upper lobe aerated on inflation. The post-operative course was uneventful, and at a follow-up examination four months later there was no radiographic evidence of recurrence of the tumour.

PATHOLOGICAL EXAMINATION.—

Macroscopically.—The tumour weighed 520 g. and measured 12 cm. in diameter. The appearance of the cut surface is shown in *Fig.* 580.

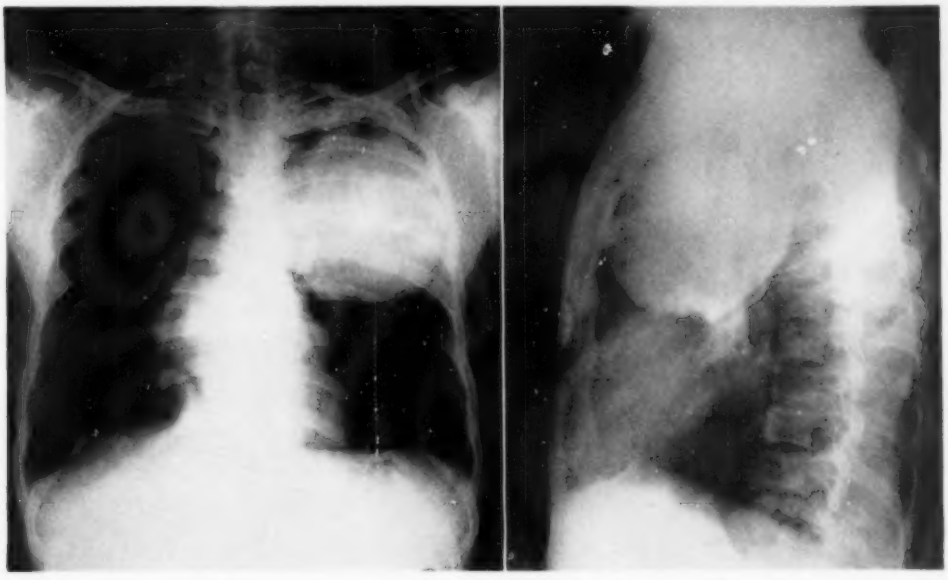
Microscopically.—Carcinoid type of adenoma (*Fig.* 581).

DISCUSSION

In an extensive discussion on bronchial adenoma by Foster Carter (1941) the statement is made: "A

bronchial adenoma arises invariably in one of the larger bronchi and there is no record of this tumour occurring in the periphery of the lung." Since that date cases of the peripheral type of lesion have been described and it is in these descriptions that the reported large bronchial adenomas are to be found. Maier and Fischer (1947) reviewed 5 cases in which an adenoma was found arising from a segmental bronchus, and it is interesting to note that their largest lesion occurred in a 16-year-old negress, the diameter of her lesion on radiography being 6 cm. Viking (1952) reported a case in which an adenoma of 6·5 cm. was removed by right lower lobectomy. Frazer (1957) reported one of similar size in his review of 12 cases. Good (1953) stated that the maximum size of an adenoma seen on radiography was 9 cm. in diameter.

The peripheral adenoma, apart from its tendency to develop to extremely large dimensions, differs in its clinical presentation from the centrally placed one. Hæmoptysis is uncommon, pulmonary suppuration secondary to obstruction of a major bronchus does not occur, and the tumour is not usually visible bronchoscopically. This is due to the fact that the peripheral adenoma bears a different relationship to the bronchus from which it arises as compared to the centrally placed one. Although anatomically a



A B

FIG. 578.—A, Postero-anterior and B, lateral radiographs taken in 1959.

FIG. 579.—The tumour is seen presenting in the interlobar fissure. The Duval forceps are on the edges of the upper and lower lobes.

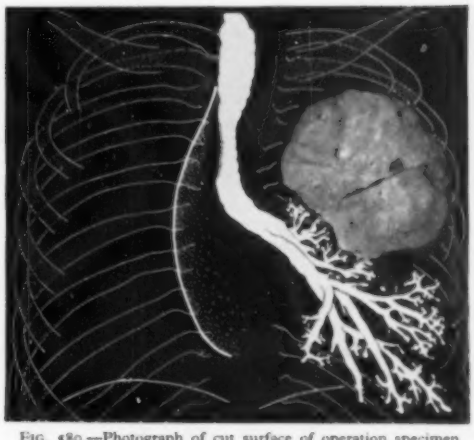


FIG. 580.—Photograph of cut surface of operation specimen superimposed on tracing of bronchogram.

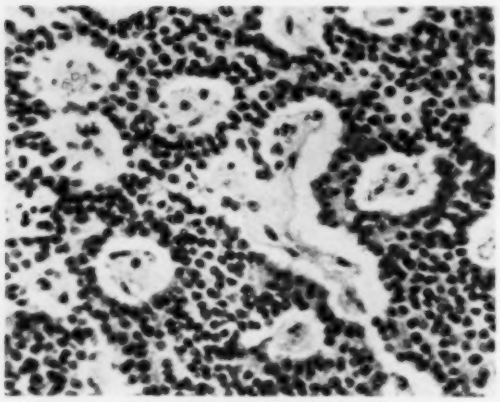


FIG. 581.—Photomicrograph showing the characteristic appearance of the carcinoid type of bronchial adenoma.

centrally placed adenoma is rarely entirely inside the bronchial lumen, and commonly assumes an iceberg formation with a small intrabronchial portion and a larger extrabronchial one, in the case of a peripheral adenoma the whole tumour may be outside the lumen of the bronchus (Price Thomas, 1954). This state of affairs was clearly demonstrated in the case reported above, and it accounts for the fact that it was possible to remove the adenoma by enucleation rather than by resection of pulmonary tissue. A previous report of an adenoma being removed by this method has not been found in the available literature.

SUMMARY

1. A giant adenoma of the bronchus of the peripheral type is described.

2. Previously reported large adenomas are recorded.

3. The case reported illustrates the fact that a peripheral adenoma can be removed by enucleation without resection of pulmonary tissue.

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URETHRAL CARCINOMA FOLLOWING URETHROPLASTY

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PRIMARY carcinoma of the urethra is uncommon and has been classified for clinical purposes as carcinoma of the anterior and carcinoma of the posterior urethra, the anterior urethra being the urethra distal to the bulb, the posterior signifying the bulbous and membrano-prostatic urethra. This classification is useful in considering the treatment and prognosis of the two types. McCrea and Furlong (1951) and Riches and Cullen (1951), in extensive reviews of the subject, adopted this classification and showed that as a rule carcinoma of the anterior urethra can be treated more easily by radical amputation and has a better prognosis than cancer of the posterior urethra.

The case reported is one of carcinoma of the urethra at the penoscrotal junction, i.e., anterior urethra, following reconstruction of the urethra five years previously for severe stricture. In addition a primary carcinoma of the glans penis occurred two years before the carcinoma of the urethra became manifest. The author has been unable to find a similar case amongst the 250 cases previously reported.

CASE REPORT

S. B., aged 59 years, a cotton spinner, first attended the out-patients' department at Withington Hospital on Jan. 3, 1951, complaining of difficulty in starting micturition and a poor, thin stream tending to deviate to one side. He had suffered from gonorrhœa in the first world war, and in 1946 had been treated for a urethral stricture by bouginage and had been circumcised. Nine weeks before he was seen he had had an attack of pain in his right loin associated with acute retention of urine, which had subsided after temporary suprapubic bladder drainage had been carried out at Ashton Infirmary, Lancs. When seen his sole complaint was dysuria.

ON EXAMINATION.—He was an apparently fit man. The cardio-respiratory system was normal. Blood-pressure was 130/80. The lower pole of the right kidney was palpable; shotty inguinal glands were present on both sides. A urethral stricture could be palpated in the glans adjacent to the external meatus. The scrotal contents were normal. A diagnosis of anterior urethral stricture with a possible right hydronephrosis was made.

On July 5, 1951, meatotomy and bouginage were performed (Mr. T. Moore). The terminal ¾ in. of the urethra was slit open from the external meatus. Urethral bouginage was carried out with some difficulty. Only Lister's sounds, up to 2/5, could be passed into the bladder owing to multiple strictures of the penile urethra.

On July 9 an intravenous pyelogram showed good normal renal outline, with no hydronephrosis. Blood-urea was 26 mg. per cent.

The patient was discharged to the out-patients' department after a few days. He continued to complain of a poor stream and constant dribbling and was re-admitted to hospital.

FIRST OPERATION (Nov. 12).—*Urethroplasty and suprapubic cystotomy* (Mr. T. Moore). A 2/5 metal sound was passed into the bladder. The ventral surface of the penis was then incised longitudinally by cutting down on to the metal sound, the urethra being laid open as far as the bulb. A suprapubic cystotomy was performed and a fine red rubber catheter inserted retrogradely from the bladder along the urethra to the tip of the penis. The skin edges on the ventral surface of the penis were sutured together over the catheter as in the second stage of a Denis Browne repair of a hypospadias. Suprapubic and

scrotal drains were inserted. No skin was used to increase the urethral lumen.

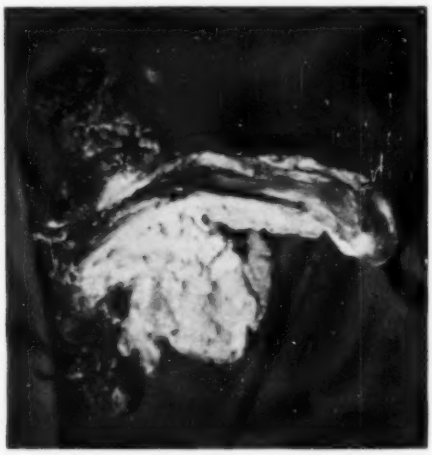
The catheter splint was finally removed in one month and the patient was able to pass urine normally when he was discharged to the out-patients' department on Dec. 15.

He attended the out-patients' department regularly for bouginage at fortnightly intervals, Lister's sounds up to 16/19 being passed easily. On January 5, 1955 he was referred again for admission. A tiny wart on his glans penis had been noted for several years when he had attended for bouginage. The wart had been regarded as trivial until three months prior to re-admission when it

FIG. 582.—Diagram taken from notes showing position of penile wart in December, 1954.

had been noticed to be slowly getting larger. When the patient was re-admitted, it was described as ¼ in. in diameter (*Fig.* 582).

SECOND OPERATION (Jan. 6, 1955).—*Excision of wart from glans penis* (Mr. T. Moore). The pathological



A

report stated: "The specimen consists of a piece of skin and warty nodule ½ cm. in diameter. Sections show a papillary form of an early well differentiated epidermoid carcinoma. There is extensive infection of underlying supporting stroma." (*Fig.* 583.)

The patient was referred back to the out-patients' department and again attended regularly for bouginage until October, 1956, when a peri-urethral abscess developed at the peno-scrotal junction. He was re-admitted on Oct. 13, 1956.

THIRD OPERATION (Oct. 15, 1956).—*Bouginage and curettage of urethral fistula and biopsy* (N. F. K.). The urethra was dilated up to 12/15. The peri-urethral abscess and sinus were curetted and granulation tissue removed. A No. 6 gum-elastic catheter was passed into the bladder along the urethra and the abscess cavity packed with Vaseline gauze.

Biopsy report: "Section shows granulation and fibrous tissue infiltrated with eosinophils, plasma cells, lymphocytes and occasional polymorphs indicative of subacute and chronic pyogenic inflammatory reaction."

The urethral fistula persisted in spite of prolonged urethral drainage.

FIG. 583.—Histology of penile wart. (× 5.)

B

FIG. 584.—A, Cross-section of specimen, penis and scrotum, removed Jan. 14, 1957. Note carcinoma of the urethra present at the base of the penis. B, Anterior view of specimen which shows the urethral sinus from which three biopsies were taken to establish the diagnosis.

FOURTH OPERATION (Nov. 9).—*Second excision of urethral fistula and bouginage* (N. F. K.). Metal sounds up to 13/15 were passed and the sinus, with surrounding fibrous tissue at the peno-scrotal junction, was excised down to the urethra. A No. 8 gum-elastic catheter was inserted along the urethra into the bladder. Again the urethral fistula persisted.

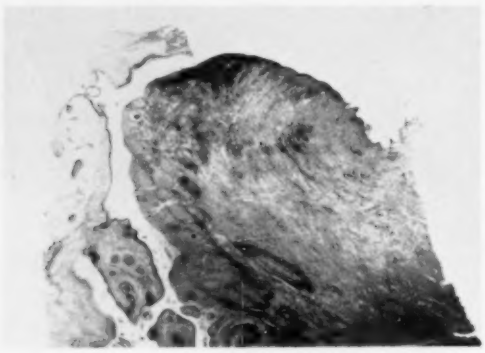
FIFTH OPERATION (Dec. 13).—*Third excision of urethral fistula and biopsy* (N. F. K.). The urethra was dilated to 12/14. The fistula was excised and sent for biopsy. A No. 20 Stewart Foley catheter was inserted into the bladder.

Biopsy report: "Section shows a well differentiated keratinized squamous epithelioma".

The treatment of this patient, who now was known to have a carcinoma of the urethra, was discussed with Dr. Dobbie and Dr. R. Paterson of the Christie Hospital.

Manchester. It was agreed that surgical treatment was indicated for this patient's condition.

SIXTH OPERATION (Jan. 14, 1957).—*Radical excision of penis and scrotum* (N. F. K.). The penis and scrotum were encircled by an incision round the base of the scrotum and root of the penis, extending laterally into both groins. The subcutaneous tissue and glands in the groins were reflected inwards, the inguinal canals opened, and the spermatic cord divided at the internal abdominal ring. The crura were removed from the pubic arch and



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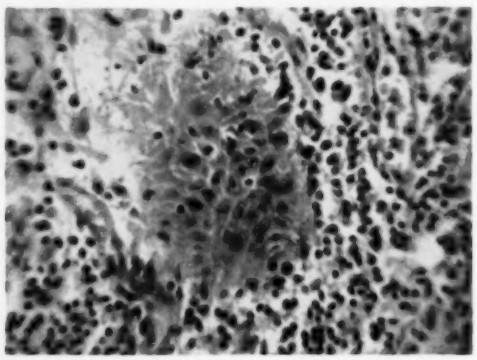

B

FIG. 585.—Histology of carcinoma of anterior urethra. A, × 5. B, Same tissue as A showing early infiltrative activity in centre of field. (× 150.)

FIG. 586.—Appearance of perineum six months after radical operation.

the urethra displayed below the triangular ligament and divided 1·0 cm. distal to this. The mass of inguinal subcutaneous tissue and glands, crura, penis, and scrotum were removed. The divided urethra was sutured to the posterior margin of the wound and the anterior end of the wound was closed, leaving a central area approximately 2 × 3 cm. open to avoid tension in the skin-flaps. A No. 20 Stewart Foley catheter was inserted into the bladder. The specimen removed is shown in *Fig.* 584.

Pathological Report.—Penis and scrotum: at the base of the penis is a firm white ulcerated tumour mass 3 cm. in diameter. There is no evidence of tumour in the scrotum and testicles.

Microscopical examination: Section from the tumour mass shows a papillary form of a well-differentiated squamous epithelioma with many cell-nests. There is gross infection of the tumour in some areas (*Fig.* 585).

The patient progressed satisfactorily. A small skin-graft was applied to the granulating area adjacent to the urethral opening on Feb. 8, 1957. He was discharged to the out-patients' department on March 22, 1957, and has remained well since. He has attended for review regularly. Further bouginage has not been required. He is now working full-time as a green-keeper. His weight has increased by half a stone. He was last seen in September, 1960. *Fig.* 586 shows a photograph of the patient's pelvic region after his operation site had healed.

DISCUSSION

Aetiology.—The association of stricture of the urethra with carcinoma has been well established. Hotchkiss and Amelar (1954) state that 48 per cent of cases of carcinoma of the urethra have been preceded by a stricture; Zaslow and Priestley (1947) quote 25 per cent of cases of carcinoma associated with a urethral stricture. Riches and Cullen (1951) thought that this factor may be overstressed, but found that 4 patients out of 9 with carcinoma of the posterior urethra had suffered from stricture.

The possibility of some additional effect due to trauma to the urethral mucosa produced by regular bouginage for stricture must be considered. In the case reported bouginage was carried out approximately 100 times. Reports of regular bouginage for stricture in cases of carcinoma of the urethra are frequently found (Uhle and Holfelner, 1952; Kreutzmann and Collof, 1939). More severe trauma may also be followed by carcinoma. Nansen (1951) and Cooke (1952) both reported patients with urethral injury with fracture of the penile shaft who later developed urethral carcinoma. In many cases infection connected with a stricture or a peri-urethral abscess is recorded (Kirkman, 1949; Uhle and Holfelner, 1952). There seems little doubt that stricture, its associated bouginage and infection, and possibly injury, can in some cases stimulate the urethral epithelium to form carcinoma.

It is interesting to note how rare it is for carcinoma of the bladder to be implanted into the urethra, especially in view of the common occurrence of carcinoma of the bladder and the subsequent frequent cystoscopy which these cases require. However, Riches and Cullen reported 5 cases of possible transplantation of seedlings from carcinoma of the bladder

to form carcinoma of the urethra in a series of 15 male cases of carcinoma of the urethra. But McCrea and Furlong (1951), in their comprehensive survey of the literature, quote only 5 per cent of cases of carcinoma of the urethra as being transitional-celled, which they regarded as arising directly from the prostatic urethra and not due to transplantation.

Pathology.—In the case reported the carcinoma of the urethra was a well-differentiated squamous-cell carcinoma with many cell-nests. This is the commonest type of carcinoma in the urethra, and nearly all carcinomas in this area have squamous characters.

Another important point in this case is the possible aetiological relationship of the papillary carcinoma of the glans penis to the carcinoma in the reconstructed urethra. Although the carcinoma of the glans penis was removed about 18 months before the occurrence of the carcinoma at the peno-scrotal junction in the reconstructed urethra, it is not considered that there was any transplantation of tumour tissue. Dr. Stent (pathologist) reports as follows: "(i) The histology of the first tumour is an early form of carcinoma presenting as a white nodule; (ii) it is not infiltrating the subepithelial stroma to any extent, and (iii) it would have metastasized, I think, by now via lymphatic channels into the deep inguinal nodes or external iliac nodes if it had not been removed completely. The second tumour gives the typical picture of a squamous epithelioma of the urethra with a papillary tendency. It is a well-differentiated slow-growing type with calcification in some areas, and it is arising in the portion of the urethra where these lesions commonly occur. Direct implant would, I think, be most unlikely in view of the early phase of the first lesion and the time interval between the second lesion occurring."

Diagnosis.—Diagnosis of carcinoma of the urethra is often made too late for effective treatment to be given (Dean, 1956). This is partly due to the rarity of the condition. In the case reported here, ten weeks elapsed between obvious clinical signs suggestive of carcinoma, i.e., urethral obstruction, swelling at peno-scrotal junction, and persistent urethral fistula, and confirmation by positive biopsy. It must be noted, however, that a negative biopsy result was obtained about ten days after the case was referred for in-patient treatment, the diagnosis of carcinoma being suspected at that time.

The importance of submitting for histological examination sections of the wall of any peri-urethral abscess which is incised cannot be stressed too strongly. More than half of all the cases of carcinoma of the urethra have formed a peri-urethral abscess, or had a urethral fistula associated with them (McCrea and Furlong, 1951).

Treatment.—Most cases of carcinoma of the anterior urethra require operative treatment. As a rule these tumours are not sensitive to irradiation. Although Flocks (1956) records 2 cases of carcinoma of the anterior urethra treated successfully by local diathermy coagulation, the consensus of opinion in the literature undoubtedly is in favour of total amputation of the penis (or subtotal amputation in early carcinoma of the distal urethra) (Kreutzmann and Collof; Zaslow and Priestley; Kirkman; McCrea and Furlong; Riches and Cullen).

The inguinal glands, if enlarged, should be removed *en bloc* with the penis and scrotum. Although there may be some doubt whether these glands are the seat of metastasis, their removal adds little to the extent of the operation and should be carried out if they are suspect. Metastasis may occur also into the external iliac and other intrapelvic glands. Flocks suggests performing a biopsy on these glands at the time of the block dissection; if metastasis has occurred possibly deep X rays to the pelvis may help.

If the penis is removed orchidectomy should be performed as well (Riches, 1958; Kirkman, 1949). Although some American authors (Kaufman and Goodwin, 1953; McCrea and Furlong, 1951) state that emasculation does not increase the recovery rate, orchidectomy removes an impediment to micturition in a patient with a perineal urethrostomy and, furthermore, by abolishing libido it also removes a source of psychological frustration. Even if the scrotal skin is required to repair perineal defects, as described by Uhle and Holfelner (1952), the testicles could still be removed.

Treatment of carcinoma of the anterior urethra by radical excision gives the only hope of prolonged survival, but unfortunately only a minority of cases—18 per cent (McCrea and Furlong)—are seen early enough to enable this to be carried out. However, many cases of carcinoma of the urethra are of low malignancy (Huggins and Curtis, 1928) so that once the condition is diagnosed, a determined effort should be made to render the patient fit for radical surgery, which may give a gratifying result in what appears to be a most unfavourable case.

SUMMARY

1. A case of carcinoma occurring in a reconstructed urethra is described.

2. The aetiology is discussed.

3. Radical surgical removal of the penis and scrotum is recommended for carcinoma of the anterior urethra.

My thanks are due to Dr. L. Stent for many investigations carried out on this patient in the Pathology Department, and for her assistance during the writing of this paper.

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GASTRIC CARCINOMA FOLLOWING GASTRO-ENTEROSTOMY AND PARTIAL GASTRECTOMY

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INTRODUCTION

Any large enough series of gastric carcinomas will contain patients who have previously had a gastro-enterostomy or partial gastrectomy for a peptic ulcer. A recent run of such cases was the stimulus for the present study. Although diagnosis is difficult and there are other points of interest, few papers on the subject have been published.

MATERIAL

From 1949 to 1958 inclusive, 19 patients who had previously had a gastro-enterostomy or partial gastrectomy presented with a carcinoma of the stomach; the diagnosis was confirmed in 15 by operation, in 3 by autopsy, and in 1 by endoscopic biopsy. During this 10-year period there were 445 radical or palliative resections for gastric carcinoma. Some patients with obvious metastases were never admitted to the ward or radiographed, so that the total number of patients with gastric carcinoma who attended is uncertain. If this is estimated as probably 900–1000, the 19 patients with a previous gastro-enterostomy or partial gastrectomy will be about 2 per cent of all gastric carcinomas. This can be compared with the figure of 1·1 per cent of 1623 cases reported by Pack and Banner (1958) from the Memorial Cancer Center at New York. The difference is not statistically significant.

RESULTS

Table I gives the main details. The blood groups are what might be expected in any series of peptic ulcers. There are 17 men and 2 women, and their ages range from 40 to 76 years. Ages at the time of the original operation range from 26 to 46 years for the 13 patients with a gastro-enterostomy, and from 34 to 65 years for the patients who had had a partial gastrectomy. The intervals between gastro-enterostomy and the diagnosis of carcinoma of the stomach range from 18 to 37 years; the intervals after partial

Table I.—Analysis of Cases to show Original Lesion, its Surgical Treatment, and the Site of Origin of Carcinoma

Case	Sex	Age (years)	Original Lesion	Original Operation	Site of Origin of Carcinoma	Blood Group
1	M.	62	Gastric ulcer	Gastro-enterostomy + wedge excision	Pyloric antrum	A
2	M.	62	Duodenal ulcer	Gastro-enterostomy	Cardia	O
3	M.	66	Duodenal + gastric ulcer	Gastro-enterostomy; previous wedge excision	Body	O
4	M.	66	Duodenal ulcer	Gastro-enterostomy + suture of perforation	Prepyloric	B
5	M.	58	Gastric ulcer	Gastro-enterostomy + wedge excision	Pyloric antrum	O
6	M.	66	Prepyloric ulcer	Gastro-enterostomy	Pyloric antrum	O
7	M.	47	Duodenal + gastric ulcer	Polya partial gastrectomy	Cardia	B
8	M.	66	Duodenal ulcer	Polya partial gastrectomy	Cardia	A
9	M.	76	Duodenal ulcer + pre-pyloric ulcer	Gastro-enterostomy	Cardia	O
10	F.	69	Duodenal ulcer	Billroth-II partial gastrec-tomy	Fundus	A
11	M.	52	Gastric ulcer	Polya partial gastrectomy	Stoma	O
12	M.	53	Duodenal ulcer	Gastro-enterostomy	Stoma	O
13	M.	55	Duodenal ulcer	Gastro-enterostomy; later partial gastrectomy	? Anterior wall of gastric stump	A
14	M.	40	Duodenal ulcer	Gastro-enterostomy	Stoma	O
15	M.	69	Gastric ulcer	Partial gastrectomy	Cardia	B
16	M.	54	Duodenal ulcer	Gastro-enterostomy	? (Extensive)	A
17	F.	72	Duodenal ulcer	Gastro-enterostomy; later restoration of anatomy	Region of old stoma	?
18	M.	70	Duodenal ulcer	Gastro-enterostomy	? (Extensive)	?
19	M.	67	Gastric ulcer	Partial gastrectomy	Fundus	O

gastrectomy range from 2 to 36 years. In 2 cases the interval between partial gastrectomy and the development of a carcinoma was less than 5 years. In both cases the carcinoma apparently originated near the cardia; in one the original lesion was a duodenal ulcer, in the other a gastric ulcer; microscopic sections taken at the original operation were reviewed, but nothing was seen to suggest that any carcinoma was present at the first operation.

Nine of the twelve gastro-enterostomies were done for duodenal ulcer; in one of these cases a co-incidental prepyloric ulcer was left in situ, and in another a gastric ulcer had previously been treated by wedge excision. Three gastro-enterostomies were carried out for gastric ulcer, and two of these were accompanied by wedge excision of the ulcer.

Four of the seven partial gastrectomies were done for duodenal ulcer, including one case in which gastro-enterostomy had previously been done; in one of these cases a gastric ulcer had been noted and had healed. Three partial gastrectomies were done for gastric ulcer and the ulcer was removed in each case.

Diagnosis tended to be delayed, and only 9 of the present 19 cases were operable; of these, 2 had metastases within 18 months, 4 are known to have died within 3 years, and 3 are still alive.

DISCUSSION

The first symptoms of gastric carcinoma are often the result of slight mechanical obstruction, and hence the prognosis is better for neoplasms originating near the pylorus or cardia than for those of the mid-body. After a gastro-enterostomy, carcinoma of the antrum is relatively silent and produces obstruction late. Less significance is also attached to anæmia after a preceding gastric operation. Clinical diagnosis is thus often impossible, and unfortunately radiology is also difficult and unreliable. Excess of mucus and reflux of bile, etc., make it impossible to get good mucosal relief films, and a partial gastrectomy stump is often indistensible, as barium empties through the stoma as fast as it is swallowed. Narrowing and distortion of the distal part of the stomach beyond a gastro-enterostomy are also no proof of a neoplasm; a similar appearance can result from a combination of disuse, inflammatory swelling of the mucosa, and adhesions. If no record of the previous operation is available, the radiologist may report a previous gastro-enterostomy as a partial gastrectomy, and not realize the significance of the failure to visualize the antrum. Gastroscopy may also fail if it is impossible to distend the stomach with air. Finally, as in *Case* 1, even laparotomy may be misleading if an infiltrating lesion of the lesser curve of the pyloric antrum is buried in a dense mass of adhesions to the undersurface of the liver.

It has been suggested that peptic ulcer patients have an increased liability to gastric carcinoma, and also that the chronic gastritis which is an invariable finding after operation predisposes to carcinoma. There is no evidence in favour of this in the present material. Doll, Avery Jones, and Buckatzsch (1951), in a population survey of the London area, found that 1·1 per cent of their subjects over the age of 45 years had previously undergone surgery for a peptic ulcer, other than for perforation. This is not significantly different from our findings. In addition, 10 of the 13 gastro-enterostomies in this series had their gastro-enterostomy at The London Hospital in the period 1923–33. At this time a number of surgeons were interested in gastric surgery and very large numbers of gastro-enterostomies were being done, 1058 in the 5 years 1920–4. On the whole, the operation was successful, at least for a time, and the patients were grateful. They might, therefore, be expected to come back to the same hospital when symptoms recurred. Fresh cases, on the other hand, are more likely to be referred to one or other of the neighbouring regional hospitals, which have grown in importance in the last twenty-five years.

Helsingen and Hillestad (1956) followed up 222 cases of partial gastrectomy for gastric and duodenal ulcers. They concluded that there was no increased incidence of carcinoma in the patients who had had a partial gastrectomy for a duodenal ulcer, but that those who had had a partial gastrectomy for a gastric ulcer had a threefold increase in comparison with the general population in the same age-groups. In this series, 10 patients had had their operation for a duodenal ulcer, 6 for a gastric ulcer, and 3 for a duodenal ulcer with an associated gastric ulcer or scar. In the 1058 gastro-enterostomies from 1920 to 1924, 501 were done for gastric ulcers and 557 for duodenal ones. There is thus no evidence in this series that a gastric ulcer is more likely than a duodenal ulcer to be followed by a cancer.

If chronic gastritis from a preceding gastric operation predisposed towards carcinoma, the carcinoma might be expected to arise near the stoma where the gastritis is maximal. Freedman and Berne (1954) collected 55 cases of stomal carcinoma from the world literature and added 3 more from Los Angeles; they concluded that carcinoma originating at the stoma was relatively rare. This is contradicted by Pack and Banner (1958), who found 13 out of 19 cases in the stomal region. In the present series, 3 cases were thought to arise in the stomal region and a fourth developed in that part of the stomach which had formed the stoma until 8 years previously, when the gastro-enterostomy had been undone and the normal anatomy restored. In the absence of any evidence that patients with a gastro-enterostomy are particularly susceptible to carcinoma, it is difficult to attach any significance to these figures. The growth tends to be so advanced by the time the patient comes to operation that the stoma is often inevitably involved. There is also the possibility that the growth originating in the region of the stoma is more likely to cause early symptoms, and hence to be removed by radical operation and find its way into a pathological museum.

SUMMARY AND CONCLUSIONS

In an estimated 1000 patients with gastric carcinoma, 445 of whom had a gastric resection, there were 19 patients who had had a previous gastro-enterostomy or partial gastrectomy. There is no evidence that a preceding gastric operation predisposes towards a carcinoma, or that patients who had their first operation for a gastric ulcer are more

liable to carcinoma than those who had it for a duodenal ulcer.

The diagnosis of gastric carcinoma after a preceding gastric operation is difficult and easily missed. The possibility must always be kept in mind, especially when symptoms recur after a long silent period. Dysphagia may be due to peptic œsophagitis or to an early carcinoma. Anæmia is a common late sequel of partial gastrectomy, but it may also be the first sign of a new lesion. A weight record should be kept as a matter of routine and any unexplained loss of weight should be taken seriously.

Acknowledgements.—I would like to thank the surgical staff of The London Hospital for permission to analyse their cases. My special thanks are due to Mr. J. E. Richardson and Dr. Denys Jennings for much help and encouragement.

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REPAIR OF EPIGASTRIC INCISIONAL HERNIA

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MOST surgeons who operate in the upper abdomen meet from time to time large ventral herniæ occurring after epigastric incisions. Farquharson (1955) reminded us that "there is a wide defect in the musculature, with smooth and regular margins which are easily defined. The hernia takes the form of a diffuse bulge through the defect; it reduces spontaneously as soon as the patient lies down, and there appears to be no risk whatever of strangulation. This type of hernia can be controlled fairly well by a belt fitted with a suitable pad, and the patient is usually satisfied with such treatment—which is fortunate, since operative repair may be a matter of the greatest difficulty."

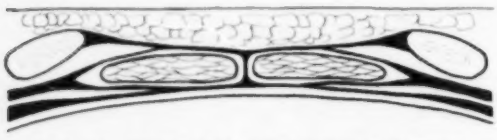

FIG. 587.—Diagram of the normal anatomy in the upper epigastrium.

Gibson (1916) thought it was possible to close even the largest post-operative hernia by the use of relieving incisions in the anterior sheath parallel to the midline suture line. In 1920 he reported 8 successful cases treated by releasing incisions made before or after suturing of the refreshed fascial edges, the first done "in 1914 on the spur of the moment in an effort to give a patient a competent abdominal wall because she was a physical training instructor". When seen six years later there was no recurrence, and the functional result was perfect.

Watson (1938), in cases of traumatic herniæ of the linea alba, advocated overlapping broad flaps of fascia reinforced on each side by additional flaps of fascia from the anterior sheath of the rectus muscle.

Mair (1948) also advised, as a reinforcement, a reflected flap of anterior rectus sheath 3 or 4 in. long and 1–2 in. broad.

Wells (1956) reported his method of repair by lateral incision and medial displacement of the anterior rectus sheath on both sides with overlap of the two displaced sheaths. He also mentioned that "tension of the anterior rectus sheath is invariably greater than that of the posterior sheath".

This paper offers an explanation of the reason for this tension, and demonstrates a repair based on anatomical principles.

FIG. 588.—Diagram showing the anatomy of an epigastric incisional hernia. The broken lines show the position of the incisions made through the anterior sheath.

ANATOMY

In the epigastrium the anterior sheath is composed, for the most part, of the aponeurosis of the external oblique muscle which in this area arises from the costal margin, and also of the anterior lamina of the aponeurosis of the internal oblique (*Fig.* 587). The posterior sheath is composed, for the most part, by the aponeurosis of the transversus muscle and by fascia arising from the posterior lamina of the internal oblique. Both these latter muscles have a long muscle span to their origins, and hence are able to stretch more easily than the external oblique with its shorter muscle distance.

For the past ten years I have been using a repair which has successfully closed large epigastric incisional herniæ (*Table I*). The repair is based on the following principles:—

1. In epigastric incisional hernia, the hernia is not due to a muscle defect, but occurs because the muscle belly has been pulled laterally by retraction of the joined anterior and posterior sheaths (*Fig.* 588).

2. Just as releasing a curtain loop allows a curtain to fall straight, so muscle, if unimpeded, tends to lie in a straight line. A vertical incision through the external oblique aponeurosis, near the lateral border of the rectus muscle, thus releases the rectus sheath, allowing the rectus muscle to move easily in or near to the midline so that both bellies of this muscle can be approximated in the midline with the minimum of tension.

Table I.—Repair of Epigastric Incisional Herniæ

Patient	Sex	Cause of Hernia	Date of Repair	Age at Repair	Remarks
S. L.	M.	Wound sepsis after partial gastrectomy, July 14, 1948	July 25, 1949	48	No recurrence Sept. 1959
J. H.	F.	Cholecystectomy, Nov. 14, 1949	July 7, 1950	57	No recurrence Sept. 1959. Partial gastrectomy Oct. 1954
J. B.	F.	Cholecystectomy, Nov. 14, 1949	July 27, 1950	58	Ventral hernia recurred following incision of abscess in lower end of scar May 22, 1954
F. H.	M.	Cholecystectomy, June 20, 1949	Aug. 30, 1950	46	No recurrence when last seen in 1955
H. J.	M.	Partial gastrectomy, April 10, 1951	March 14, 1952	41	No recurrence Sept. 1959
C. M. H.	F.	Partial gastrectomy May 31, 1951	Oct. 28, 1952	60	No recurrence Sept. 1959. Cholecystectomy July 1959, through right paramedian incision
M. C.*	M	Wound sepsis after partial gastrectomy, Sept. 3, 1952	July 14, 1953	50	No recurrence Sept. 1959
G. S.	M.	Sepsis following high right paramedian incision, May 10, 1954	Feb. 10, 1955	51	Secondary hæmorrhage into wound followed by sepsis
T. H. A.	M.	Wound sepsis after partial gastrectomy, Oct. 3, 1952	Oct. 31, 1955	59	No recurrence Dec. 1959
B. B.	M.	Wound sepsis after partial gastrectomy, Oct. 8, 1951	Sept. 17, 1957	55	No recurrence Sept. 1959
H. H.	M.	Wound sepsis after partial gastrectomy, Mar. 26, 1954	Feb. 3, 1958	51	No recurrence Sept. 1959
W. J.	M.	Repair of perforated duodenal ulcer, May 10, 1947	May 5, 1958	69	No recurrence Aug. 1959
A. W.	M.	Midline incision for perforated duodenal ulcer, Dec. 19, 1947	May 21, 1958	37	No recurrence Sept. 1959
G. S.	M.	Sepsis after repair of ventral hernia, Feb. 10, 1955	Dec. 30, 1958	54	Secondary hæmorrhage into wound on 9th day. No recurrence March 1959
J. C.	M.	Secondary suture after perforated duodenal ulcer, May 9, 1954	May 4, 1959	62	No recurrence Sept. 1959

* This patient states that he has had a small lump appear opposite his navel on three occasions. It only occurred while he was straining in a squatting position at work, and each time he has been able to replace the lump by pressure with a finger when he stood up. Recent careful examination failed to reveal any obvious defect at this site, but he must have had a small protrusion of retroperitoneal fat through a defect in the posterior sheath near the lateral edge of the rectus.

OPERATIVE TECHNIQUE

After elliptical excision of the old scar tissue and some of the excess skin, skin-flaps are raised as far as the costal margin. The medial boundary of the rectus muscle is defined on either side of the hernia by a small incision, and the anterior sheath separated from the posterior sheath with scissors. While tension with three or four artery forceps is applied on the medial aspect of the anterior sheath, its lateral border is incised a finger's breadth medial to the costal margin in the upper epigastrium and the same distance from the lateral edge of the rectus muscle in the lower epigastrium.

The rectus muscle, with its adherent anterior and posterior sheaths, can now be brought to the midline. When both recti are freed the posterior sheaths from either side can be brought together with a continuous chromic catgut suture, plicating the redundant peritoneum in the process. If the peritoneum has been opened it can be closed as a separate layer. The anterior sheaths are now approximated, using interrupted figure-of-eight linen sutures. The skin is closed with interrupted linen sutures, using alternate vertical mattress and simple sutures. Meticulous hæmostasis usually obviates the need to drain, but if the skin is loose and serum collection a possibility, suction drainage, as advised by Wells, is indicated. If local anæsthesia is used, the bleeding is minimal.

DISCUSSION

The success which Wells has had with his operation may be explained by his use of the lateral incision

of the anterior sheath. This incision allows the recti to approximate, and once more to lie in the position Nature intended for them. The posterior sheath arises from such a length of muscle, encircling almost

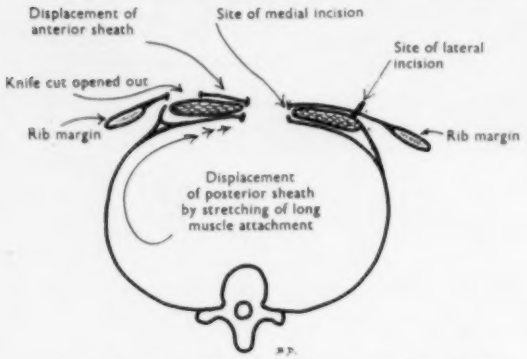
Displacement of anterior sheath
Site of medial incision
Site of lateral incision
Knife cut opened out
Rib margin
Rib margin
Displacement of posterior sheath by stretching of long muscle attachment

FIG. 589.—Diagram showing anatomy of the posterior sheath.

the entire abdominal cavity, that it exerts no restraining influence in this inward movement (*Fig.* 589).

Gibson has remarked that "the surprising feature in the after-result of these cases is the lack of weakness of the abdominal wall where the fascia gapes as a result of being pulled away". Immediately after the operation, however, the lateral weak spot is covered not only by thinned-out muscle, but posteriorly has the internal oblique and transversus muscle fascia as a firm support. In my series there is only one case of herniation through this area (*see Table I*). Recently I had to perform a cholecystectomy on a patient for whom I repaired an epigastric incisional hernia seven years ago, using the technique described above. At operation it was found that the anterior sheath had grown over the bare muscle gap in a thin but definite layer, and the rectus muscle appeared to be of normal thickness.

SUMMARY

A method of repair of epigastric incisional hernia is offered, with an anatomical explanation for its effectiveness.

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WILMS' TUMOUR: LOBECTOMY FOR PULMONARY METASTASIS

A CASE REPORT

BY LEONARD HAAS AND ANTHONY D. M. JACKSON

THE prolonged survival of a patient following treatment of an uncomplicated Wilms' tumour (nephroblastoma) is no longer unusual (Gross and Neuhauser, 1950; Ng and Low-Beer, 1956), but it has not previously been recorded following surgical removal of a pulmonary metastasis.

The case described below has several unusual features—the lung metastasis was slow-growing, and the patient survived for more than six years after its removal. Unfortunately he succumbed to a local recurrence with widespread abdominal dissemination, but not until 11½ years after the original nephrectomy.

CASE REPORT

David B. (3874/52), born Jan. 23, 1942, was first seen at the age of 4½ years on account of a three months' history of left-sided abdominal pain. A large tumour was felt in the left loin, and there was no excretion of dye by the left kidney on intravenous pyelography. Laparotomy at another hospital in September, 1946, disclosed a large retroperitoneal tumour arising from the left kidney. This tumour was considered to be inoperable and, because of its vascularity, no biopsy was carried out.

The patient was transferred to The London Hospital, where the clinical findings were confirmed. Radiography of the lungs showed no evidence of metastases. In December, 1946, a course of deep X-ray therapy was commenced; irradiation was given to the upper abdomen with anterior and posterior, directly opposed, parallel fields, field size 15 × 15 cm. (220 kV., 15 mA., focus-skin distance 50 cm., filtration 0·5 cm. copper plus 1 mm. aluminium). The dose was initially 50 r and was later increased to 100 r giving a total incident dose (with back-scatter) of 650 r per field, spread over 16 days.

Following radiotherapy the abdominal tumour was considerably reduced in size and a further operation was performed on Jan. 21, 1947, by the late Mr. Charles Donald.

AT OPERATION.—The tumour was found to arise from the upper pole of the left kidney. It was adherent to the under surface of the diaphragm, although there was no actual invasion of neighbouring structures. The kidney, together with the tumour, was dissected free with some difficulty, and the whole mass finally removed.

PATHOLOGICAL REPORT.—The specimen consisted of the left kidney (10 × 6 × 3 cm.) showing several smooth yellow nodules both on the surface and at the hilum. On section, collections of well-encapsulated nodules occupied the upper pole and central part of the kidney, with a further mass at the hilum. The cut surface of the nodules was firm and showed patches of hæmorrhage. The ureter was not identified. The histological appearances were those of a Wilms' tumour. In view of the subsequent clinical course it is of special interest that the tendency towards differentiation of tubules was more marked than usual.

After operation the whole upper abdomen was irradiated with a wide-field bath, one posterior and two anterior

fields, each 20 × 20 cm., with the same factors as in the pre-operative irradiation. The total incident dose was 1060 r per field, spread over 21 days.

The patient was discharged in March, 1947, and he remained well and gained 18 lb. in weight over the next 4 years. Radiographs of the chest were reported as normal until February, 1951, when a small, solitary, rounded opacity was noted in the upper lobe of the right lung. The

FIG. 590.—Radiograph of chest, showing a well-defined solitary rounded opacity in the right upper lobe.

possibility of a secondary deposit was considered and the patient was kept under close clinical observation. By December, 1951, he was still free from any symptoms, and the opacity had only slightly increased in size (*Fig.* 590). Very carefully reviewed scrutiny of the previous radiographs revealed that a shadow in the right upper lobe had actually been present, although only just detectable, as early as April, 1949. Serial Mantoux tests were negative up to a concentration of 1–100. After due consideration it was decided that this lesion was most likely to be a solitary secondary deposit, and that in view of its slow growth, the good general condition of the patient, and the absence of deposits elsewhere, radical treatment was justified. He was therefore readmitted in February, 1952. He had gained a further 7½ lb. in the previous year, and there were no abnormal physical signs on examination.

SECOND OPERATION.—A right transpleural thoracotomy was performed on March 4, 1952, by Mr. Vernon Thompson. The upper lobe of the right lung contained a solid tumour and was completely removed. There were no obviously enlarged glands in the mediastinum.

PATHOLOGICAL REPORT.—The specimen consisted of the upper lobe of the right lung. In its lower posterior border was a lobulated, firm, white nodule (2·8 cm. in diameter) with a granular cut surface (*Fig.* 591). There was no involvement of the pleura overlying the tumour.

Histological section of the tumour showed masses of tubules lined with a tall columnar or cuboid epithelium supported by a stroma of collagenous tissue. In places the tubules were replaced by solid masses of polygonal cells; mitoses were not seen. Although the growth as a whole was well defined, a few peripheral extensions invaded the adjacent lung parenchyma. The appearances were those of secondary nephroblastoma (*Fig.* 592).

PROGRESS.—During the next three years the patient remained in good health and gained 11 lb. in weight. However, in April, 1955, he began to complain of malaise, flatulence, and lack of appetite; he had lost 4 lb. in weight in the previous six months.

On physical examination a hard fixed mass was felt below the costal margin on the left side. Radiographs of the chest, skull, and long bones did not reveal any evidence of secondary deposits, and an intravenous pyelogram of the right kidney was normal.

In May, 1955, he was submitted to further deep X-ray irradiation of his upper abdomen, anterior and posterior fields, field size 20 × 15 cm. (250 kV , 15 mA., focus-skin distance 50 cm., filter 1 mm. Cu and 1 mm. Al). The total incident dose was 1600 r per field over the course of

FIG. 591.—Upper lobe of right lung, bisected to show the lobulated firm, white nodule in the periphery of the lower and posterior border. For comparison with *Fig.* 590.

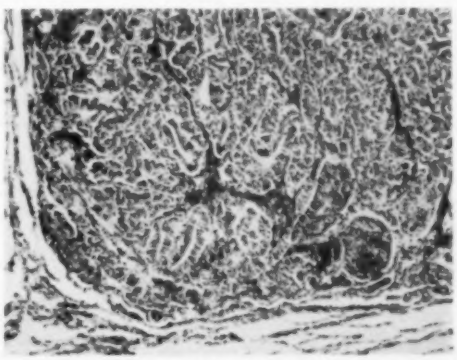

FIG. 592.—Microscopical appearance of the secondary deposit shown in *Fig.* 591. Masses of tubules lined with tall columnar or cuboid epithelium supported by a stroma of collagenous tissue.

15 days. The tumour had by then become much smaller and could no longer be palpated.

THIRD OPERATION.—A laparotomy (carried out by Mr. Hermon Taylor) revealed, however, an irregular mass, 15 cm. in diameter, arising from the posterior abdominal wall. This tumour was adherent to the liver, stomach, spleen, and pancreas, and was obviously a local recurrence of the nephroblastoma; surgical excision was impossible. As a precaution against further dissemination no biopsy was taken. Post-operatively another course of radiotherapy was given, with a total incident dose of 2500 r in 15 days.

For the next 15 months the patient remained well and gained 3 lb. in weight, but in October, 1956, he again

became ill and ceased to gain weight. By March, 1957, the abdominal tumour had again become palpable, but, once more, disappeared following radiotherapy (Telecobalt 60, 3900 r in 24 days). From this time, however, the boy's condition slowly deteriorated, and in the early part of 1958 a barium meal showed an extrinsic filling defect of the upper part of the stomach, with numerous indentations in the transverse colon and splenic flexure indicating further intra-abdominal secondary deposits. During August, 1958, there were clinical signs suggesting secondary deposits in the liver, and the patient died suddenly on Aug. 13.

At Autopsy.—The cardiac end of the stomach was adherent to the spleen and in this area there was infiltration with a small central ulcer. There was massive invasion of the liver by secondary deposits which had perforated the capsule in places, and had infiltrated the pancreas and diaphragm. There was no evidence of any recurrence in the lungs.

DISCUSSION

Both the primary tumour and the pulmonary metastasis showed particularly slow growth, the latter having been present for at least three years before its removal. Both tumours showed a marked tendency towards tubular differentiation, but were highly radio-sensitive. No doubt the histological features of this unusual tumour, combined with the close combination of surgery and radiotherapy, account for the prolonged survival of this patient.

There are other recorded instances of prolonged survival after treatment for pulmonary metastasis from a Wilms' tumour (Kerr, 1939; Garrett and Mertz, 1953; Ng and Low-Beer, 1956; Kerr and Flynn, 1956; Lattimer, Melicow, and Uson, 1958). All these reports refer to patients treated by radiotherapy, which seems to be the accepted treatment for this complication. However, radiotherapy alone cannot be relied upon completely to eradicate pulmonary metastases even in the case of radiosensitive tumours. Kerr and Flynn (1956) reported a series of 28 cases of Wilms' tumours, 12 of whom had lung metastases. All received radiotherapy, but in 5 patients the lung lesion reappeared within a short space of time.

Surgical removal of pulmonary metastases in malignant disease other than Wilms' tumour has been practised for many years. Seiler, Clagett, and McDonald (1950) collected 62 such cases, 23 of which were well at the time of being reported on. Two patients had survived for 10 years or more, 7 for periods ranging from 3 to 10 years, and 14 patients for periods varying from several months to 2 years after resection. Denk (1951) reported 6 cases, 5 of whom survived for periods ranging from 3 months to 2 years. A patient reported by Mannix (1953) was alive and well 2 years following removal of a pulmonary metastasis. All these workers came to the conclusion that any patient whose primary malignant disease appears to have been successfully treated and who subsequently develops a single pulmonary metastasis should be given the benefit of further surgical treatment. It seems reasonable to apply this to cases of Wilms' tumour. The progress of the patient reported above supports this conclusion in spite of the eventual outcome.

SUMMARY

An unusual case of Wilms' tumour is described.

The microscopical features showed marked tendency to differentiation and the rate of growth was unduly slow.

The total survival time from diagnosis to death was 12 years, and the survival time from diagnosis to the first abdominal recurrence was 8½ years.

A solitary pulmonary metastasis appeared approximately 2½ years after diagnosis and was present for over 3½ years before surgical removal, and the patient survived for 6½ years after lobectomy without further pulmonary metastasis.

Acknowledgements.—We wish to thank Dr. Kenneth H. Tallerman for permission to report the case of this patient who was admitted under his care; and also Dr. Walter Shanks, Mr. Hermon Taylor, and Mr. Vernon Thompson, who were all actively concerned in the treatment of this boy. The pathological reports were kindly supplied by Professor Dorothy Russell, who also gave valuable assistance in the preparation of this paper.

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BILATERAL MALIGNANT CYSTOSARCOMA PHYLLODES

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A SURVEY of the literature reveals that only 1 case of bilateral malignant cystosarcoma phyllodes has been recorded. Reich and Solomon (1958), in their report of this condition, present a case which has many similarities to one encountered at this hospital.

CASE REPORT

S. T., an African female patient aged 22 years, was admitted to hospital on Feb. 26, 1951. She had had one child five years previously and another two months prior to admission. Shortly after the commencement of her second pregnancy she noticed a small lump in the left breast. The lump began to enlarge, and seven months prior to admission she noted a slight blood-stained discharge from the nipple on that side, which cleared up spontaneously within a week. Three days prior to admission the breast became painful, considerably more enlarged, and hot to the touch. She felt feverish.

The systematic history was non-contributory.

Gynæcological: Menses C16 $\frac{2-3}{30}$. No dysmenorrhœa, no history of premenstrual tension in the breasts. Had not had a period since the birth of the youngest child.

ON EXAMINATION.—Her temperature was 100° F., pulse 100, respiration 34, blood-pressure 100/60 mm. Hg. The patient was well nourished, obviously ill, and very toxic. General examination revealed nothing abnormal in the various systems.

The left breast was massively enlarged to almost three times the size of the right breast. The skin of the breast was œdematous and hot to the touch. On palpation there was moderate tenderness, and there seemed to be several large fluctuant areas interposed with firm rubbery breast tissue.

There was no discharge from the nipple. Radiography of the chest was negative and a hæmatological examination revealed a Hb of 12·3 g. per cent and a white blood-count of 10,700.

A diagnosis of breast abscess was made and at operation about 2 pints of pink purulent fluid were released and all loculations were broken down. The breast tissue itself was found to consist of friable necrotic material, some of which was taken for histological examination.

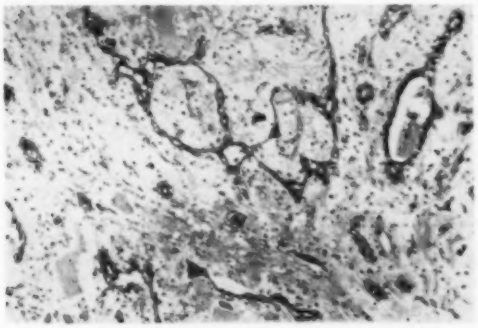

FIG. 593.—Showing the histological features of an intracanalicular fibro-adenoma. There is marked hyperplasia and increased cellularity of the stroma. H. and E. (× 60.)

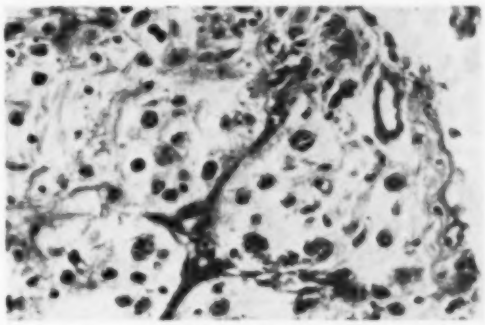

FIG. 594.—Higher magnification to show the stromal cellularity. H. and E. (× 240.)

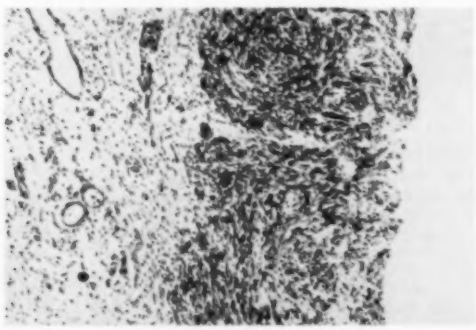

FIG. 595.—Focus of fibrosarcomatous change. H. and E. (× 60.)

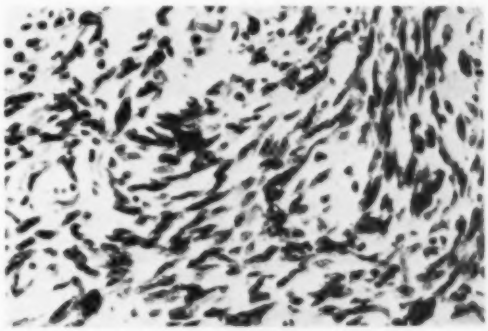

FIG. 596.—Higher magnification of *Fig.* 595. H. and E. (× 240.)

FIGS. 593–596.—THE LEFT BREAST

HISTOLOGICAL REPORT.—"Section of this breast biopsy shows marked proliferation of the stromal tissue. Myxomatous and œdematous regions alternate with territories of densely hyaline collagenous tissue and areas of more cellular structure. The myxoid tissue is composed of stellate cells and fibres forming a loose network. Scattered throughout the stroma are clefts and ducts lined by a flattened or cuboidal type epithelium. The latter also lines polypoid projections of the hyperplastic stroma. Cyst-like spaces are often seen. The canaliculi are markedly distorted. In some areas the epithelial element is hyperplastic and multi-layered. Parts of the tumour are necrotic and these show considerable infiltration by neutrophils and plasma cells. Histologically this tumour presents the appearances of an infected intra-canalicular fibro-adenoma in which there is more than usual overgrowth of both the epithelial and connective-tissue elements. The hyperplasia of the latter is, however, most striking and this, together with the pronounced cellularity, favours a diagnosis of cystosarcoma phyllodes. There is no evidence of malignant change." (*Figs.* 593, 594.)

The breast then appeared to fungate, with proliferation of pink fleshy tissue within the wound, and a further biopsy was carried out.

The histological report was as follows:—

"Section of this specimen shows undoubted cystosarcoma phyllodes. The stroma is hyperplastic and very cellular, showing cells that are round, spindle-shaped, and often bizarre with several nuclei. The stroma is also infiltrated by plasma cells. Some areas show fairly prominent epithelial hyperplasia and there are foci where this is forming bud-like projections. At one part in one of the sections the stromal hyperplasia has taken on a more cellular and pleomorphic appearance. Here the cells are arranged in sheets and whorls, show frequent mitoses and marked vesicularity of the nuclei. This area is one of fibrosarcomatous transformation." (*Figs.* 595, 596.)

In view of the above findings a simple mastectomy was carried out on Mar. 24. The wound healed by primary intention and the patient was then given radiotherapy to the site of the mastectomy.

She was finally discharged from hospital on May 23 with instructions to attend the out-patient department at regular intervals.

Three further pregnancies followed without incident.

ON READMISSION.—The patient was readmitted on April 16, 1957 when two months pregnant. She stated that a lump appeared in the remaining breast two months prior to becoming pregnant, and since the advent of the pregnancy the lump had almost doubled its size.

Examination revealed a well-circumscribed lobulated mass in the surviving breast. The mass was mobile and about 2 in. in diameter. Both firm and cystic areas were noted. Numerous veins coursed in the skin over the surface of the tumour. The previous mastectomy site was clear of metastases and no palpable glands were noted in either axilla or supraclavicular regions.

Radiological examination of chest and skeleton was negative. A clinical diagnosis of fibro-adenoma was made and at operation a well-encapsulated, lobulated, partly cystic and partly solid, tumour was removed.

The histological report was as follows: "Microscopic examination of these breast sections shows very prominent

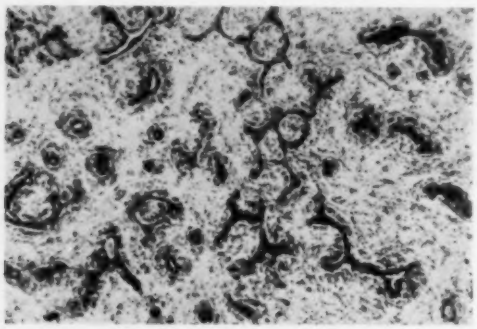

FIG. 597.—Marked epithelial and stromal proliferation. H. and E. (× 60.)

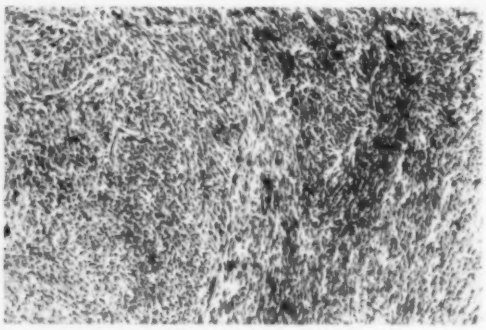

FIG. 598.—Area of frank fibrosarcoma. H. and E. (× 60.)

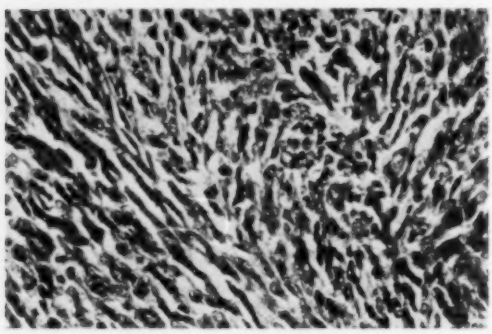

FIG. 599.—Higher magnification of *Fig.* 598. (× 240.)

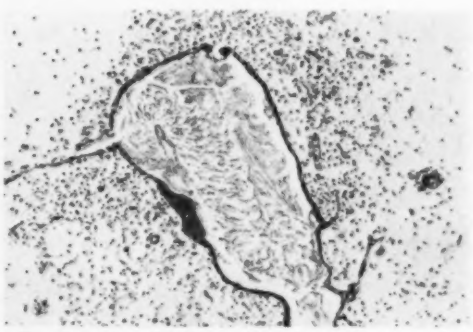

FIG. 600.—Large keratin cyst lined by stratified squamous epithelium. H. and E. (× 60.)

FIGS. 597–600.—THE RIGHT BREAST

ductal hyperplasia with marked proliferation of the myo-epithelial cells, the latter showing frequent mitoses and occasionally streaming off into the stroma. There is also considerable stromal hyperplasia with moderate cellularity and frequent multinucleated giant cells. The stroma shows an occasional polypoid appearance. The features are those of a highly active intracanalicular fibro-adenoma showing foci of cystosarcoma phyllodes. Although the tumour is very cellular there is no evidence of malignant neoplasia." (*Fig.* 597.)

The patient was discharged from hospital after an uneventful post-operative course and continued to attend the out-patients' department.

Another pregnancy in 1958 was complicated by the fact that yet another lump occurred in the breast. This lump again enlarged towards the end of the pregnancy and one month after the child was born the patient was readmitted.

ON READMISSION (Feb. 5, 1959).—At this stage the lump had been present for three months. It was again lobulated, mobile, and well circumscribed, but this time was situated in the upper outer quadrant and about 2 in. in diameter. There was no evidence of extramammary spread.

An excision of the mass was again carried out and the histological report was as follows: "The specimen consists of a mass of fat 8 cm. in diameter containing three nodules 1½ cm., 3½ cm., and 3 cm. in diameter respectively. They are all firm and white in colour. Microscopical examination of two of the nodules shows the histological structure of cystosarcoma phyllodes. The third nodule shows frank fibrosarcoma. The tumour cells are spindle-shaped and arranged in whorls, and show marked mitotic activity with considerable pleomorphism (*Figs.* 598, 599).

"A further feature of interest is the presence of foci of massive epidermoid metaplasia with keratin cyst formation. (*Fig.* 600)."

In view of the findings a simple mastectomy was performed on Feb. 21, and after an entirely normal post-operative course the patient was discharged. Radiotherapy was not administered. Since discharge the patient has been seen at regular intervals in the out-patients' department. When last seen in September, 1959, eight and a half years after the occurrence of the first tumour, she was fit and well, there being neither clinical nor radiological evidence of metastases.

DISCUSSION

Both this patient and that of Reich and Solomon (1958) show a relationship between pregnancy and the occurrence of cystosarcoma phyllodes. Though most of these tumours occur in females of childbearing age, and Reich and Solomon state that because of this it is difficult to evaluate the role of pregnancy in the activation of cystosarcoma phyllodes, it is nevertheless of interest that, in both cases, both breasts became involved in association with pregnancy.

The spread of the disease in the malignant variant of cystosarcoma phyllodes is generally blood-borne, and therefore simple as opposed to radical mastectomy has been employed in the treatment.

Pathologically cystosarcoma phyllodes is regarded commonly as a giant variant of the intracanalicular type of fibro-adenoma in which the connective-tissue component is obviously the active ingredient and may frequently, by its great overgrowth, mask the epithelial element (Evans, 1956). Treves and Sunderland (1951) state that the two main criteria used to establish the identity of the tumour are the pronounced overgrowth and increased cellularity of its connective-tissue element.

Hill and Stout (1942) are of the opinion that cystosarcoma phyllodes always arises in an established fibro-adenoma and that fibrosarcoma originates *ab initio* from the connective-tissue stroma of the breast. Adair and Hermann (1946) feel, however, that malignant transformation of the connective-tissue component of a cystosarcoma phyllodes may certainly occur. This view receives confirmation from the sequence of events in our subject.

There are only 10 instances of bilateral cystosarcoma phyllodes recorded in the literature (Crile, 1938; Reed and Hiebert, 1942; McDonald and Harrington, 1950; Lester and Stout, 1954; Reich and Solomon, 1958), and only 1 that showed bilateral malignant transformation (Reich and Solomon, 1958). In point of fact, true malignant transformation in cystosarcoma phyllodes is rare, approximately 30 cases having been reported (Reich and Solomon, 1958).

A further remarkable feature of the pathology of this case is the presence of massive epidermoid metaplasia with keratin cyst formation in the tumour removed from the right breast. This has been recorded only once previously (Salm, 1959).

SUMMARY

The second reported case of bilateral malignant cystosarcoma phyllodes is described.

The first tumour was removed eight and a half years ago. The growth of both lesions appeared to be accelerated by pregnancy. The second tumour removed showed, in addition, massive epidermoid metaplasia with keratin cyst formation. This finding has been reported only once previously.

Acknowledgements.—We wish to thank Mr. S. Kleinot, Senior Surgeon, Baragwanath Hospital, for his encouragement; the Superintendent for permission to publish; and the Director of the South African Institute for Medical Research for facilities granted. We are also grateful to Professor B. J. P. Becker for his advice. Mr. M. Ulrich, of the photographic department of the South African Institute for Medical Research, produced the photomicrographs.

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MANDIBULECTOMY FOR ADAMANTINOMA

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In modern surgical literature there are numerous cases reported of excision of the lower jaw and replacement with a prosthesis—for example, Hamilton (1959). This was attempted in the case here reported, but unsuccessfully. However, the end-result remained surprisingly good and the case is reported to show that a satisfactory cosmetic and functional effect can be achieved without a prosthetic replacement—and that it is probably the best line of management to undertake outside specialized units.

CASE REPORT

S. R., an Indian female aged 17 years, was admitted (Sept. 3, 1959) to this Surgical Unit on transfer from another hospital in the Fiji group on account of a massive swelling on the left side of the lower jaw. The patient stated that some time over a year before, she had had toothache in the left lower jaw, which had persisted and been associated eventually with swelling of the area. For this reason she had been admitted a year previously to the local hospital, where an operation on the left lower jaw was performed. The nature of this operation is uncertain for there are no adequate notes available, but presumably it was some form of incision and curettage. In any case there was no permanent improvement and within a short time of the operation the swelling had reappeared and was increasing in size; pain had been a feature for the two months preceding transfer to this unit.

FIG. 601.—Photographs of patient, showing extent of swelling.

FIG. 603.—The prosthesis.

Examination showed notable deformity due to a great distension of the left lower jaw affecting both the horizontal and ascending rami and extending just across the midline to the healthy side of the jaw (*Fig.* 601). The tumour showed a bluish tinge and was cystic in nature. Egg-shell crackling could be elicited. The whole area was most tender to palpation. All teeth were present in the lower jaw, although they were tender and loose in the tumour segment. The incision of the previous operation was slightly curved just below the horizontal ramus of the affected side and about 3 in. in length. She could shut the mouth completely, but could only get it half open.

Dr. H. E. Knowles reported on the radiographs as follows: "There is a large expanding tumour of the left mandible involving the horizontal and ascending rami.

FIG. 602.—Radiograph showing tumour of the left mandible.

Its multilocular appearance and well-defined margins are consistent with an adamantinoma. There is at least one apical abscess on the right side." (*Fig.* 602.)

A biopsy was not done, for it was felt that the radiological diagnosis was backed up by the clinical features of the case; in any case the patient was having a lot of pain and it was clear that if it was at all possible the tumour, which meant the left half of the mandible and beyond, had to be resected. However, I had not seen this done and therefore a period of contemplation and study of the literature was indicated.

During this period of waiting the pain steadily increased in intensity and the temperature rose to 100° and above. The acute pain and temperature resolved when the tumour burst into the mouth in the region of the lower left fourth and fifth teeth. The pain, although not so acute, still persisted in a severe degree. It was thought that this severe pain might be due to some pus dammed up in the tumour and the patient was therefore taken to theatre (Sept. 22) for examination under anæsthesia and drainage of the pus collection. Radical surgery was not

contemplated at this stage on account of the presence of infection. Further, we felt inadequately 'briefed' at this time to proceed with the definitive surgery. In fact, we found no free pus and simply confirmed that the left side of the jaw was completely replaced by a multilocular tumour. It was evident at this examination that there was a fracture running right across the cyst to the angle of the jaw. This fracture was complete and probably the cause of much pain.

FIG. 604.—Facial appearance after mandibulectomy and removal of prosthesis.

All the teeth in the affected side of the jaw and diseased teeth elsewhere were extracted during this time under local anæsthetic. The intention was to proceed to straight resection without prosthetic replacement, but the dental officer who extracted the teeth took a keen interest in the case and offered to make a prosthesis on the basis of the radiographs and measurement of the normal side of the mandible. This prosthesis was made during this period and is illustrated to give some idea of the amount of mandible resected (*Fig.* 603) (in fact, the eventual resection included about 1 in. more mandible than this). It was made of acrylic and incorporated a screw to go into the apposing medulla and two drill-holes to take fixation wires at the medial end.

AT OPERATION.—By this time a plan of campaign had been worked out and on Oct. 14 the operation was proceeded with under endotracheal anæsthesia through a cuffed tube and with the mouth well packed off. A curved incision was made from the lobe of the ear to just beyond the point of the jaw and the skin-flaps including platysma raised. The initial move was to ligate the external carotid artery and this took the greatest part of the operation time, for no very good reason apart from some fibrosis from the previous operation tying down the tissues under the upper flap. The medial end of the incision was deepened down to normal feeling bone at the medial end of the tumour and the normal bone was divided subperiosteally with a Gigli saw. The divided end was then swung outwards and then, with traction maintained, the mandible, or at least what remained of it, was shelled out of the soft tissues. Large sheets of periosteum remained intact and wherever possible the dissection was continued in the subperiosteal plane. There was little difficulty in the operation after the external carotid artery had been found and ligated, although the condyle broke across in removal at the end of the operation and this was removed separately. The prosthesis was then fitted in and seemed to settle fairly well into position after the muscles and soft tissues generally had been closed around it. The jaw seemed to have a full range of movement and to be stable enough when moved passively at the end of the operation, which in all lasted 4½ hours.

PROGRESS.—The patient soon recovered consciousness on return to the recovery ward, but the jaw never worked satisfactorily and, in fact, it stuck in the half-open position with very little movement either way. Intravenous therapy was continued and feeding commenced through an intragastric Levine's tube. The whole jaw slewed to the normal side and it became clear that the prosthesis was too short and was not going to work. Therefore on Oct. 19 the patient was taken back to theatre and the prosthesis removed without difficulty at a short operation. It was clear at this operation that the prosthesis had not been made long enough, with the result that it had slewed to the normal side by its fixation to the normal mandible and the prosthetic head had thus come out of the left temporomandibular joint. The opportunity was also taken at this time to remove another tooth and a further ½ in. of mandible, for inspection showed that the original resection had left a minute portion of the tumour behind in the centre of the medullary cavity. The mucosal lining of the mouth was opened into only at this inner end of the resection, and this opening was closed by interrupted plain catgut sutures.

There was some infection around the prosthesis and after it was removed the soft tissues were closed by interrupted chromic catgut sutures around a corrugated rubber drainage tube. Despite this precaution the wound broke down and discharged some pus, but it healed satisfactorily by granulation, leaving a surprisingly good scar.

Progress after removal of the prosthesis was rapid. Soon after rousing from the anæsthetic the patient was able to drink water in sips and within ten days was taking a light diet. She experienced no further pain after the immediate post-operative period and was, in fact, ready for discharge home on Nov. 7, but stayed in hospital until Nov. 17 awaiting clinical photographs and shipping arrangements. Radiography on Nov. 6 was reported as follows (Dr. H. E. Knowles): "The whole of the left mandible has been removed, but there now appears to be some calcification (? new bone forming) in the region of the ascending ramus."

Her appearance is normal and there is no evidence cosmetically that over half of her mandible is missing.

(*Fig.* 604.) She eats well with the remaining portion of the mandible which has occlusion with the maxilla, the outer edge of the lower teeth on to the inner edge of the upper teeth. Histopathological examination (Dr. M. Gosden) confirmed the diagnosis of adamantinoma (*Fig.* 605).

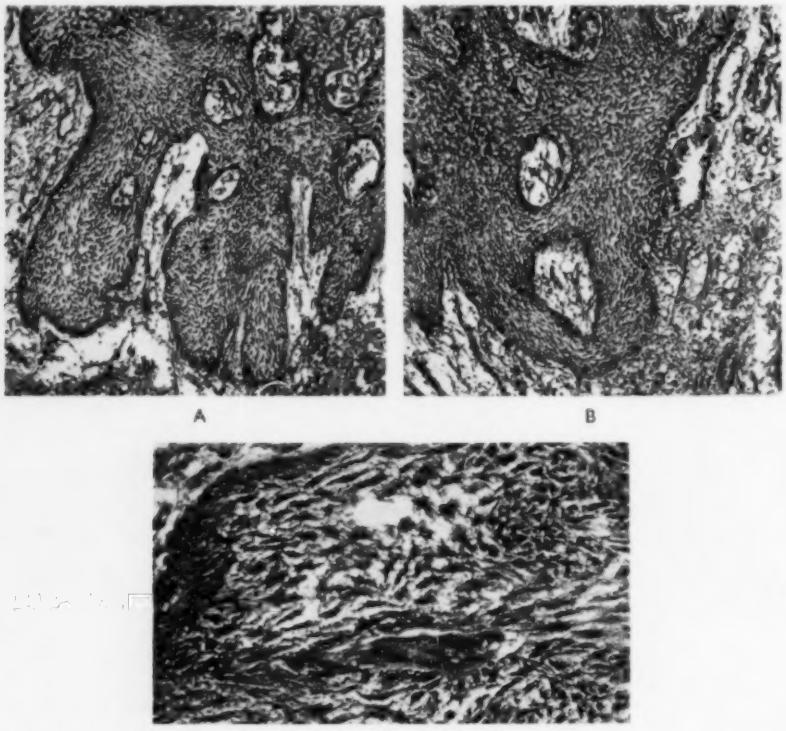

FIG. 605.—Broad columns limited externally by cellular palisades enclosing grossly vacuolated sheets of stellate cells. (A, B, × 100; C, × 375.)

DISCUSSION

Some hesitation was felt before proceeding to resection in this case of extensive adamantinoma on account of the deformity and malfunction anticipated. This anxiety was unnecessary as it turned out, for the functional and cosmetic results have been satisfactory. Although prosthetic replacement is the ideal, special experience and skill are needed for the manufacture of the prosthesis, and it is suggested that outside specialized centres resection without replacement is likely to be the correct management. As is recognized, early adequate resection is the key to successful surgical treatment of adamantinomata, but this case, like most cases reported, had undergone previous inadequate surgery.

Subperiosteal resection, as carried out here, possibly carries a greater risk of recurrence, but at the same time promises a useful amount of re-formation of bone; for this reason it would seem to be justifiable to accept the small chance of recurrence where there is a worthwhile amount of periosteum remaining and a good subperiosteal layer of cleavage. The key to the easy performance of the operation was early anterior division of the mandible (Simpson, 1957), which made easy its subsequent removal by shelling it out of the soft tissues using sharp and blunt dissection on bone.

The period of follow-up is necessarily short, for the patient comes from an outlying island, but unlike cases involving prosthetic replacement there should be no future deterioration (so long as the resection has been adequate); with a prosthesis there is always the danger of tissue reaction, with its varying sequelæ.

SUMMARY

The management of a large adamantinoma of the mandible is reported in some detail and it is suggested that resection without prosthetic replacement is the best procedure away from specialized centres.

Acknowledgements.—I wish to thank Dr. W. H. McDonald, M.B.E., Acting Director of Medical Services, Fiji, for permission to publish; and Mr. Rob Wright, of the Public Relations Office, Fiji, for the photographs.

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COARCTATION OF THE AORTA PROXIMAL TO BOTH SUBCLAVIAN ARTERIES PRODUCING REVERSIBLE PAPILLŒDEMA

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THIS history of a boy with coarctation of the aorta is recorded because of two features that are rarely seen in this disease—namely, the presence of papillœdema and the absence of a palpable pulse in all four limbs.

CASE REPORT

HISTORY.—Roger L. had a full-term normal delivery of unrelated healthy young parents. There was no difficulty in establishing respiration and no evidence of birth injury. He developed normally, although a heart murmur was discovered at 3½ years when he had measles.

At the age of 13 years he was referred to one of us (A. G. V. A.) by Dr. J. E. Russell, of Kidderminster, with the following letter: "This young lad was brought by his mother complaining that he was feeling tired and suffering from nocturnal perspiration. . . . The history does not

FIG. 606.—Artist's impression of the left retina.

suggest any cardiac decompensation. He plays all games and takes part in normal activities without dyspnœa or distress. . . . On examination I found no cardiac enlargement or thrill. A systolic murmur was present over the precordium, loudest in the aortic area and conducted into the neck vessels which were visibly pulsating to ear level. . . . All his peripheral arteries were difficult to palpate, brachials, femorals, and dorsalis pedis. . . . A possible diagnosis of coarctation was entertained, but he had no hypertension in his arms. . . ."

This exceilent report from his general practitioner was confirmed by subsequent findings. The only relevant point to add to the history was that the sweating was mainly of the head and neck. He denied suffering from headache or any trouble with his eyes. He was particularly fond of Rugby football, as well as playing tennis and cricket.

Examination, other than that of the cardiovascular system and eyes, was negative. His general condition was good, although his weight of 77½ lb. was below the mean for his age. All the peripheral pulses were almost impalpable. The blood-pressure in the arms was recorded as ? 120/? 70. The apex beat was normally situated. The second pulmonary sound was accentuated, but the other sounds were normal. There was a generalized systolic murmur, maximal in the third left interspace at the sternal border and transmitted up into the neck. Here there was vigorous arterial pulsation and a palpable systolic thrill, more marked on the left side. Examination of the fundi showed blurring of the disk margins and arterial changes (*see below*). Electrocardiography indicated systolic overloading of the left ventricle.

On these findings the child was considered to have coarctation of the aorta with an anomalous right subclavian

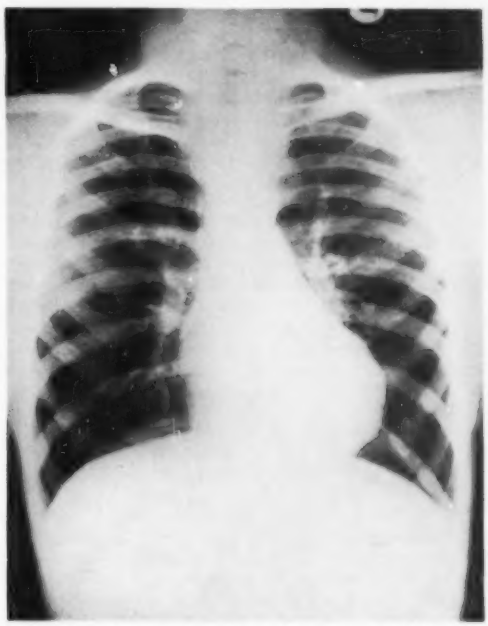

FIG. 607.—Frontal radiograph showing the rounded bulge of the left superior mediastinal border.

artery arising below the left subclavian, both of these vessels leaving the aorta distal to the coarctation.

He was therefore admitted to the Birmingham Children's Hospital under the care of Dr. Clifford Parsons for full investigation and treatment.

OPHTHALMIC FINDINGS.—There were 1½ dioptres of papillœdema in both eyes, with some scattered hæmorrhages of the left disk. The veins were full, but the striking feature lay in the arteries, which were as wide as the engorged veins (*Fig.* 606). Their calibre at first sight appeared to be irregular, but careful focusing showed that this appearance was due to differing depths of the arteries within the retinal layers as they lay in a 'corkscrew' shape. This appearance was similar to that described by Granström (1951). Visual acuity was normal, with no refractive error and normal visual fields.

RADIOLOGY.—The heart was not enlarged in its transverse diameter (cardiothoracic ratio 49 per cent). The left lower segment was rounded and the pulmonary

segment flat. On the left superior mediastinal border there was a rounded, pulsatile bulge, larger and slightly higher than the usual aortic knob (*Fig.* 607). Penetrating pictures showed that the latter was rather small and lay within the lower part of this shadow. Pulmonary vascularity was normal. The ribs (especially the 5th to 9th) had long, shallow notches on both sides.

FIG. 608.—Tracing from left oblique radiograph with barium swallow.

FIG. 610.—Composite tracing from angiocardiogram (left oblique position).

In the left oblique projection the left ventricle was prominent. The superior mediastinal vascular mass was now seen to overlie the posterior part of the aortic arch, extending above it to the level of the left clavicle (*Fig.* 608). In this view the barium swallow showed a posterior indentation of the œsophagus that corresponded to the aortic arch and, above this, a shallow indentation that corresponded to the mediastinal mass. In the frontal view the œsophagus had a normal left-sided indentation at the level of the aortic arch and at a higher level a half-shadow indentation, running obliquely upwards from left to right. In the right oblique position this was seen as a fairly small rounded posterior indentation (*Fig.* 609).

The radiological diagnosis at this stage was that of aberrant right subclavian artery (arising as the last branch of the aortic arch) together with coarctation of the aorta (presumably, in view of the clinical picture, situated above

FIG. 609.—Right oblique radiograph with posterior œsophageal indentation (arrow).

the origins of both subclavian arteries). The bulge in the left superior mediastinal border was probably due to an enlarged left common carotid artery.

Angiocardiography showed these deductions to be correct (*Fig.* 610). The right heart was normal, the left somewhat enlarged. The coarctation, well seen at 9 sec., consisted of a localized constriction in the descending part of the arch, with both pre- and post-stenotic dilatation. There were two very large common carotids; both subclavians arose immediately below the stenosis. It was evident that the descending aorta filled directly through the narrowed segment, but in addition there was a descending flow via collateral vessels from the neck. A maze of these, including the deep cervical arteries and both vertebral arteries, were first identified in the upper cervical region and their opacification subsequently *descended* to the level of the subclavian arteries.

AT OPERATION.—Under supplemented anæsthesia (Dr. A. E. Matthews) consisting of pentothal, curare, nitrous oxide, and oxygen, the chest was opened (A. L. d'Abreu) through the fourth left intercostal space. No enlarged collateral vessels were encountered. The aortic arch and upper third of the descending aorta were exposed. Two large, pulsating carotid vessels were seen; there was no innominate artery. The left side of the arch ended in a narrow coarcted isthmus, with a distinct, almost aneurysmal, bulge to the left just above it; below the coarctation was a characteristic non-pulsatile post-stenotic dilatation. From this arose a small, thin-walled, left subclavian artery in which the blood-flow was reversed, the blood passing into the descending aorta; the ligamentum arteriosum lay

opposite to this vessel. The right subclavian artery, also small and thin-walled, came off the back of the aorta, also below the coarctation, passing over to the right behind the œsophagus. The aortic intercostal arteries were normal in size but exhibited the typical tortuosity of such vessels that is seen in coarctation.

One small vessel came off the aorta above the coarctation; it was doubly ligated and tied. After the appropriate dissection and mobilization, the blood-pressure was lowered by arfonad and two Pott's clamps were placed on the aorta above the narrowing. The great vessel was then divided between them and the lower end was sutured. A reconstituted aortic homograft was sutured to the proximal end of the divided aorta and the lower end of the graft was sutured to an adequate opening made in the descending aorta after temporary clamping of the latter and of the subclavian arteries. On completion, good pulsation was seen in the descending aorta and pulses were soon palpable in all four limbs. The chest was closed in the usual way with underwater sealed drainage.

POST-OPERATIVE PROGRESS.—Immediate progress was satisfactory. Two months after operation all peripheral pulses were present, although the radials were not strong. His E.C.G. had improved. Seven months after operation he cycled 47 miles in one day and the difficulty was to prevent his over-exertion! The swelling of the disks had absorbed and the calibre of the retinal vessels had reduced, with a normal size relationship of veins to arteries. The 'corkscrew' appearance of the arteries remained.

DISCUSSION

Granström (1951) described a characteristic 'corkscrew' appearance of the retinal arteries that is often seen in coarctation of the aorta. At first sight the tortuosity appears to be associated with varying arterial width and light reflexes. These changes, however, are only apparent and are caused by the varying depth within the retina of the different parts of the 'corkscrew'.

The present subject showed this type of appearance, but in addition there was bilateral papillœdema, which was not observed by Granström. Indeed, the occurrence of papillœdema in coarctation of the aorta appears to be very rare; only one other recorded example has been found (McGregor and Medalie, 1952). This was an 8-year-old boy, and surely it must be more than coincidence that in this subject the anatomical abnormality was exactly the same as the very uncommon one described in the present case—namely, coarctation above the origins of both subclavian arteries.

The symptoms and signs were those of severe hypertension in the cerebral circuit, with completely impalpable pulses in all four limbs and a much enlarged left ventricle. No collateral vessels were detected and there was an absence of rib notching. The fundi showed hypertensive retinopathy and the arteries had "irregular zones of constriction"; in the right fundus there was papillœdema with numerous exudates and a macular star. Within a few weeks the boy developed a left facial paralysis and loss of vision in the left eye, with signs of left heart failure. An attempt at surgical relief was made, but the child died of cardiac arrest during the operation.

In a case anatomically somewhat similar, described by Brynolf, Crafoord, and Mannheimer (1958), the aorta arched behind the œsophagus. The coarctation was situated near the top of the arch, after the origin of the carotid arteries but before the origin of the subclavians. No mention was made of the retinal appearance.

In the present case, successful operation was performed before severe symptoms had developed, largely because of the astute observations of his general practitioner.

The reason for the association of such unusual features of coarctation in two subjects needs further consideration. The explanation appears to be in the anatomy of the carotid systems. When both subclavian arteries arise below the coarctation, possible collateral flow is limited. The branches of the external carotids mostly anastomose with each other and with their contralateral counterparts. There are relatively small communications to by-pass the obstruction (such as those between branches of the superior thyroid artery and the branches of the thyrocervical trunk, between the descending branch of the occipital artery and the transverse and deep cervical arteries, between the ascending pharyngeal and ascending cervical and vertebral arteries). The internal carotid arteries have no constant branches in the neck; the ophthalmic artery arises from the internal carotid almost as a straight-line continuation of the latter when it turns upwards in the carotid siphon. The carotid then communicates freely with the vertebral arteries via the circle of Willis.

Thus it appears that the most significant communication to by-pass the coarctation is likely to be through the circle of Willis, with a retrograde flow along the vertebrals into the subclavians. This supposition is confirmed by our angiocardiographic findings of a descending opacification of these vessels. The lack of collaterals at a lower level means that the high aortic pressure will be transmitted freely into the upper end of the carotids and therefore into the almost directly continuous ophthalmic arteries; here it may be the main factor in the causation of the papillœdema.

SUMMARY

Details are presented of a boy with coarctation of the aorta situated above the origin of both subclavian arteries in whom there was papillœdema. Peripheral pulses, absent in all four limbs, returned after the insertion of an aortic graft.

Both these features, the atypical situation of the aortic obstruction and the occurrence of papillœdema in coarctation, are exceptionally rare. However, a similar combination has been recorded. It is suggested that paucity of collateral circulation leads to the direct transmission of very high aortic pressure into the ophthalmic arteries and that this may be responsible for the papillœdema.

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THE EFFECT OF HUMAN TISSUES ON THE TENSILE STRENGTH OF IMPLANTED NYLON SUTURES

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NYLON was one of the earliest synthetic surgical suture materials, and observations of its behaviour in the various tissues of the body have been required to determine possible uses in surgery. Some surgeons after experiencing difficulties with nylon have banished it decisively, returning to "good-old catgut" as whole-heartedly as Halsted in his time, after catgut troubles, uttered his peremptory, "Away with the catgut", and ushered in a silken era.

But sutures, like man himself, are not all things to all men at all times in all places, though some try to make them so. Some go so far as to shun the use of any "unabsorbable" suture, and some will never use catgut. Similar disagreement about the composition of 'strings' and 'lines' is said to be found amongst those interested in rackets and rods.

Most would agree that, on the whole, nylon makes a satisfactory skin suture and catgut does not. Most would agree that nylon, along with other unabsorbable sutures, is unsuitable for use on the mucosal aspect of the urinary tract owing to calculus formation about such sutures, whereas catgut is the favourite when a suture must be left exposed to the lumen of urinary or biliary passages.

For the closure of certain abdominal wall incisions I prefer nylon of the monofilamentous variety, and for the repair of herniæ I have found monofilamentous nylon an excellent material when used as a darn in both strangulated and non-strangulated cases (Moloney, Gill, and Barclay, 1948; Moloney, 1958).

Its especial virtue I believe to be unabsorbability, so that it lies in the midst of that 'concrete' of tissue repair—the fibrous tissue which has formed in the mesh of the darn—while the darn of nylon itself acts as reinforcement to that fibrotic barricade when high strains are applied to it. This purpose is achieved only if the darn has been loosely woven at all points into sound surrounding tissues, resulting in a firm blending of these tissues with the fibrous repair of the darn. If subsequent stresses on the repair were continuous the fibrous tissues would tend to stretch and the darn would cut through the tissues, but as the natural stresses are intermittent the fibrous repair will hold, especially when supported by the darn itself, which continues thus to play a useful role as long as it remains in the tissues.

Some so-called 'unabsorbable' sutures are far from being so; thus the animal fibres, silk, and the vegetable fibres, linen and cotton, may all be engulfed and completely absorbed by the tissue phagocytes, especially in their finer gauges. But even in the thicker gauges the tensile strength of these sutures, after being exposed for some six months to the action of the tissue fluids, is reduced practically to nil. This has been emphatically demonstrated by Douglas (1949), who in an excellent series of experiments inserted considerable numbers of such sutures of varying sizes into the abdominal walls of rabbits, and after withdrawing them at varying intervals tested their remaining tensile strengths and found all of them reduced to zero within six months. As a complete contrast he found that the metals—stainless steel, tantalum, and silver—are not appreciably affected in tensile strength by six months' implantation in tissue. Douglas's findings in connexion with nylon are mentioned later.

My own observations on the action of the tissues on nylon began when I was forced by new indications to reopen, months or years later, former incisions sutured with nylon. It was perfectly clear that the fine No. 3 nylon used to suture the fat had lost much of its tensile strength, and broke at a slight pull. Suture No. 5, used to suture the peritoneum, appeared to be reduced in strength, but the thick No. 7 sutures seemed to be about as strong as when inserted. The dyed surface of the suture had been patchily decolorized, and slight loss of polish clearly indicated that the tissues had partially attacked the sutures and even absorbed traces of the nylon.

In contrast, when wounds sutured with thick braided nylon were reopened some years later there was clear evidence of the devastating effect of tissues on the numerous fine fibres composing each braided strand. Thick strands of braided nylon had not stood up to the tissues any better than silk, cotton, and linen, for, after being in situ for one or two years, the strands fragmented at the lightest touch of forceps.

It was felt that an accurate measurement of No. 5 and No. 7 gauges of monofilamentous nylon which had been removed from the tissues was necessary to determine any possible decline of tensile strength. Nylon removed from twelve wounds during the past two years provided enough material for a number of tests on lengths which had been buried in the abdominal wall for periods of from 1 to 11 years.

The need for such accurate measurement was emphasized when Catchpole (1958) asserted that he had found 80 per cent of the tensile strength of nylon lost in six months, and quoted similar views held by Harrison and Adler (1956). These assertions are probably true if referring to the very fine fibres used to make a braided suture or a sheet of the woven nylon which Harrison and Adler were considering, and their findings indicate the poor lasting qualities of such materials when implanted in the tissues. Their remarks may apply even to the fine monofilamentous fibres such as No. 3 gauge sutures. But the careful studies of Douglas (1949) showed that in rabbits the thicker varieties of nylon after six months' implantation lost only 16 per cent in tensile strength. Douglas's findings are borne out by the results of the studies presented here on lengths of nylon removed from human tissues, and detailed in the two tables.

Tables I and *II* present a comparison of the initial and final strength of nylon sutures removed from human tissues, and they show a wide variation. Even so, some definite conclusions are possible. Douglas also found a wide variability of results with nylon, for,

in his animal experiments at the end of six months, four sutures showed a clear fall in tensile strength and four were unaffected. However, in this series of sutures exposed to human tissues *all* showed some loss of tensile strength. The measurement of the exact loss is dependent on the knowledge of the initial strength of the suture, but it is clearly impossible to know this. The nearest approximation possible is the average initial strength of the batches of sutures manufactured in the year that the sutures were used; but as the records go back only to 1954, estimates only could be made of the likely initial strengths. In all measurements where the average initial strengths of the sutures were known there is a tendency to loss of strength, but it is not greater than 20 per cent (up to 5 years) with No. 7 gauge, and not greater than 23 per cent with No. 5.

In the instances where the initial strength is based on estimates only, with the No. 7—even after 11 years in the tissues—no sample had lost up to one-third of its tensile strength. Further, residual tensile strength of all those sutures is at least 8 lb., which is the average tensile strength of new catgut gauge 0–1 (B.P.).

The No. 5 nylon shows a loss of tensile strength after 11 years of a shade more than one-third, but some batches clearly withstand the years much better than that, and it appears likely that a No. 5 nylon suture after 11 years in the tissue still has a tensile strength of at least 4 lb., the equivalent of that of new catgut gauge 3/0 to 2/0 (B.P.). It is evident from this investigation that No. 5 and No. 7 nylon sutures are still having a substantial permanent effect in buttressing tissues in which they have been incorporated for 11 years.

Table I.—Comparison of Initial and Final Strengths of Nylon No. 7 Gauge Sutures removed from Human Tissues

Case No.	Initial Strength	Straight Pull Breaking Load Number of Tests	Final Strength	Percentage Loss	Time Buried
1	11·5 lb. (est.)	12	8·1 lb.	30	11 yr.
2	11·5 lb. (est.)	14	8·0 lb.	30	11 yr.
3	11·4 lb. (est.)	5	9·8 lb.	14	10 yr.
4	11·3 lb.	4	10·2 lb.	10	4 yr.
5	11·4 lb. (est.)	7	9·0 lb.	21	3 yr.
6	11·5 lb.	6	9·6 lb.	16	2½ yr.
7	11·8 lb.	11	10·5 lb.	11	2½ yr.
8	11·5 lb.	4	12·2 lb.	—	2½ yr.
9	12·5 lb.	8	10·2 lb.	18	1 yr.

Table II.—Comparison of Initial and Final Strengths of Nylon No. 5 Gauge Sutures removed from Human Tissues

Case No.	Initial Strength	Straight Pull Breaking Load Number of Tests	Final Strength	Percentage Loss	Time Buried
1	6·5 lb. (est.)	2	4·0 lb.	38	11 yr.
2	6·5 lb. (est.)	4	5·2 lb.	21	11 yr.
3	6·5 lb. (est.)	4	5·9 lb.	9	6 yr.
4	6·9 lb.	9	6·9 lb.	23	4 yr.
5	6·6 lb.	9	6·4 lb.	3	2½ yr.

CONCLUSIONS

Nylon, in multifilamentous form or fine weave of any sort, retains no tensile strength after being in the tissues for six months, and such materials add no permanent strength to a fibrous layer in which they lie.

Nylon, in the thicker monofilamentous sizes No. 5 and No. 7, retains as much as two-thirds or more of its initial tensile strength after 11 years in the tissues, and such sutures when darned across a weak area add appreciable strength to any fibrous layer in which they are incorporated.

The ideal plastic suture should lose no tensile strength in the tissues, should induce no tissue reaction, should be smooth and pliant, and further should be monofilamentous. A single strand causes sinus trouble much less frequently than the braided form (Moloney, 1958). Such material as 'terylene' and 'courlene × 3' and others not yet developed may prove better than nylon, as Catchpole (1958) suggests, but until such proof is available monofilamentous (single strand) nylon can be regarded as the most satisfactory and durable plastic material with which to reinforce the tissues.

COMMENT ON THE MEASUREMENT OF TENSILE STRENGTH

(By Mr. R. B. Christie)

All the lengths of No. 7 sutures were submitted to at least four tests, while most of them had considerably more measurements, the final figure being an average.

The tensile strength was determined on a Goodbrand yarn-testing machine with the clamps modified to break very short lengths of suture. The medium scale in pounds, 0–15, was used so that most breaks fell between 9° and 45° on the semicircular scale, the area of maximum accuracy. The ratchet mechanism was kept engaged as it is considered that in the region of 7 lb. and over the inertia of the ratchet has less influence on the result than the difficulty of reading accurately a fast falling pointer. Owing to the short lengths tested it was not possible

to use the usual wrap-around mechanism that prevents false readings due to damage by the clamps, as this requires at least 6 in. of suture; however, any low breaks near the clamps were disregarded. Also, any low breaks which were obviously due to damage by artery forceps during removal were also disregarded. Low breaks not traceable to either of these reasons were included in the average figure.

There is some irregularity of result, and it was noticeable that in many cases the lowest breaks on a strand occurred at the points where the dye had been removed, presumably by the action of the tissue fluids. There is normally a certain amount of irregularity found when testing such short strands of nylon, but this irregularity is greater than normal.

Possible Reasons for this Variability of Result with Different Strands of the Same Gauge.—

1. Damage by forceps in extracting the nylon from the tissue, the strands usually being clamped heavily to pull them out.

2. Variation between strands of nylon in the same batch and between different batches not eliminated by averaging. Nylon may vary up to 20 per cent from batch to batch, and even a few per cent from strand to strand. It is possible that improvements have been made in strength since the implantation of the 11-year-old sutures.

SUMMARY

Nylon sutures removed at re-exploration after being buried in the tissues for periods of 1–11 years were measured for tensile strength.

All fine nylon strands, as in multifilamentous sutures and woven sheets, lose all tensile strength within six months due to the action of the tissues. The thicker single strands, No. 5 and No. 7, are slowly reduced in tensile strength by the tissues, but have been shown to have appreciable and effective tensile strength 11 years later. In consequence it is inferred that when such monofilamentous sutures are used as a darn to reinforce weak fibrous unions their influence is likely to be permanent.

Acknowledgements.—I am indebted to Armour Laboratories and to Mr. R. B. Christie for making the many measurements of tensile strength of the sutures, and to I.C.I. who supplied the information back to 1954 of the initial average tensile strength of the sutures.

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SOME DIFFICULTIES AND EARLY COMPLICATIONS OF OPERATIONS ON THE ABDOMINAL AORTA BELOW THE RENAL ARTERIES

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Now that the surgery of the abdominal aorta is becoming established and more operations are being done on this vessel and its major branches, it seems opportune to record some of the difficulties, dangers, and complications which have been met in my experience of more than one hundred such operations. There is no doubt that experience reduces the hazards of any operation, not only because the technique becomes more sure, but also because the difficulties are known and so often avoided.

Whether the operation requires excision of segments of the abdominal aorta as for aneurysm, or control of blood-flow through it as for relief of aortic obstruction, many of the factors to be mentioned are common to both.

ANATOMICAL CONSIDERATIONS

1. Relationship to the Great Veins.—In the lower half of its course the abdominal aorta is closely applied to the inferior vena cava, and the proximal parts of the common iliac arteries to the common iliac veins. When there is 'periarteritis' of the aorta and its branches, which occurs particularly, but not necessarily only, with aneurysm, the veins and the arteries are so adherent that they appear as one and their separation can be exceedingly difficult. The most dangerous and most difficult vessels to separate are the right common iliac artery where it lies on the right and left common iliac veins and their confluence to form the inferior vena cava. A split or a hole in one of these major veins is difficult to repair and a frequent cause of severe blood-loss, prolonging further what is always a long and tedious operation.

To avoid this dissection it is better to occlude the branches—the internal and external iliac arteries at their origins—rather than the main trunk of the common iliac, especially on the right side. When a segment of aorta or of its major branches is the site of an aneurysm which must be effectively removed, much difficult, dangerous, and time-consuming dissection can be avoided by the method to be described below.

2. The Lumbar Arteries.—These paired vessels may arise separately or by a common trunk from the back of the aorta. I once tore off a common trunk from the wall of the aorta, and repair of the resulting 2–3 mm. hole was very difficult. If they arise separately from the posterolateral aspects of the aorta their control by bulldog clips is not very difficult, but if they arise by a common trunk this may not be so readily found although it can often be felt, and a clip or even a light hæmostat can be applied.

3. The Left Renal Vein.—This vessel crosses in front of the aorta behind the duodenum just below

the origin of the renal arteries. It must be carefully preserved and is best treated by a nylon ribbon passed beneath it. It can safely be retracted upwards a considerable distance by this method. Even with this manœuvre access may still be difficult, in which case the stump of aorta can be brought in front of the renal vein, which markedly improves access and allows it to be brought considerably nearer to the surface.

4. The Receptaculum Chyli.—This usually lies adjacent to the right posterolateral aspect of the aorta and is slightly overlapped by the right crus of the diaphragm, though it is subject to considerable variations. We had been operating on the aorta for eight years before becoming aware of the danger of this close relationship.

A 65-year-old male patient was operated on for excision of an aortic aneurysm, and, seven days later, 4 litres of chyle was aspirated from the abdomen. Aspiration was repeated on two occasions over the next two weeks, and thereafter chyle fortunately ceased to collect.

Three weeks after this operation, during dissection of the upper part of the aorta of another patient, milky fluid was seen between this and the right crus. Further search here revealed the lower end of the receptaculum chyli, which was securely ligated and no ascites resulted. It is reasonable to suppose that the chylous ascites in the first patient resulted from damage to the receptaculum, and the patient was undoubtedly fortunate to recover as he did, because chylous ascites is a very sinister condition. We now give a patient a feed of cream 3 hours before operation on the aorta and are careful to search the area behind and to the right of the aorta and in the angle between this and the right crus of the diaphragm for a 'milky' leak.

TECHNICAL CONSIDERATIONS

1. The Formation of Clot in the Blind Upper End of the Aorta or in the Iliac Arteries after Temporary Clamping.—Sometimes clot forms in the upper end of the aorta between the origin of the renal arteries and the site of the proximal clamp, and also in the iliac vessels between the clamps and the next distal vessel. This is specially liable to happen in the presence of the diseased intima which is present. To try to prevent this 10 ml. heparin in saline (25,000 units in 500 ml.) is injected into the lumina of the aorta above the clamp and the iliac arteries below the clamps, and this is repeated at intervals during the operation. When a graft is being done, or when the aorta is opened for an endarterectomy, the clamps above and below are released before final suture to eject any clot which may have formed. Should a clot pass distally in spite of these precautions —and this should be looked for at the end of the operation—it should be removed forthwith by the method of retrograde flushing with saline via the posterior tibial artery at the angle joint after opening the femoral or if necessary the popliteal artery too.

2. Leakage at the Suture Line of a Graft.—Leakage at the upper end of a graft joined to the proximal aorta may be very difficult to correct after the distal anastomosis has been done as there is insufficient slack in the graft to expose easily the posterior aspect of the anastomosis line. To avoid this embarrassment a second line of sutures should be inserted in the first place. This is not necessary below, where an end-to-side anastomosis will probably have been done and where access is easy.

3. Leaking through the Interstices of a Synthetic Graft.—All varieties of synthetic graft leak sometimes and in varying degree, some more than others, and this leakage may be a serious strain for the patient after the clamps have been removed. All grafts, except human, should be preclotted, preferably twice over, and after the upper anastomosis has been completed the upper clamp should be released for one or two beats and then after 5 min. the graft sucked and washed out with saline. When one lower anastomosis has been completed, this side should be released intermittently with a clamp on the unattached limb of the graft as near as possible to the bifurcation. At this time blood must be given rapidly by means of a transfusion pump to make up for loss and to counteract the inevitable fall of blood-pressure. The second lower anastomosis is then completed and a similar procedure carried out. When operating on a leaking aneurysm, and to avoid leakage through the graft after release of the clamps in a desperately ill patient, we use a homograft replacement. We have lost a patient operated on for leaking aneurysm from this cause.

4. Internal Herniation in relation to the Graft.—I have seen acute intestinal obstruction a week after insertion of an aortic graft. At operation obstruction was found to be due to strangulation of small intestine between the graft and the posterior abdominal wall. Resection of 4 ft. of gut was necessary, but the patient died 8 weeks later from staphylococcal septicæmia resulting from this operation. At the aortic operation it had not been found possible to close the peritoneum adequately in front of the graft. This snare can be largely avoided when a graft is done for aortic stenosis by tunnelling under the peritoneum over the common iliac arteries and lower aorta rather than by dividing the peritoneum here; when it is done for aneurysm, by the method to be described in addition.

5. Post-operative Paralytic Ileus.—It has been suggested that this frequent and troublesome complication results from the evisceration of intestines which lie unsupported so that they dilate, but I have not noticed this dilatation. Unusual paralytic ileus only seems to occur after extensive dissections in the retroperitoneal tissues, as is necessary when an abdominal aneurysm is completely excised. It does not occur after operations for obstruction of the aorta when no removal of any part is demanded. Nor does it occur after operation for aneurysm when extensive dissection is avoided as in the operation described below.

A SIMPLIFIED TECHNIQUE OF OPERATION FOR ABDOMINAL ANEURYSM

The abdomen is opened through a long left paramedian incision from the sternum to the symphysis. The abdomen is eviscerated and the intestines packed into a polythene bag clipped to the right edge of the wound. The peritoneum is incised over the aneurysm but not any lower than is necessary to mobilize the root of the mesentery with its contained vessels. The duodenojejunal flexure is mobilized, the third part of the duodenum retracted

upwards, and the left renal vein exposed. This is surrounded by nylon ribbon and drawn gently upwards. By dissection with the finger and blunt forceps the aorta proximal to the aneurysm is surrounded by ribbon. The external and internal iliac arteries on either side are then dissected and similarly surrounded. The aorta and iliac arteries are then clamped and the proximal aorta divided and anastomosed to the graft in two layers. Without further dissection the outer layers of the aneurysm are then incised and an endarterectomy is then rapidly done with the finger—the contents shell out very easily. The cavity is packed with a swab for a few minutes, then any bleeding points are sutured as in Matas's endo-aneurysmorrhaphy. Tunnels beneath the peritoneum over the common iliac vessels are made and the limbs of the graft led through these and anastomosed distally. The outer layers of the wall of the aneurysm are stitched back over the graft, which now lies almost hidden.

This technique obviates the difficult dissection of the great veins and so shortens the operation significantly and also reduces the risks of subsequent herniation and paralytic ileus.

SPONTANEOUS PERFORATION OF THE COMMON BILE-DUCT IN INFANCY

By J. H. JOHNSTON

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SPONTANEOUS perforation of the common bile-duct is an affliction which appears to be peculiar to infants in the first few weeks of life. The condition, although rare, has features which are sufficiently constant and characteristic to suggest that it may be regarded as a clinico-pathological entity.

CASE REPORT

A female infant was admitted to hospital in December, 1959, at the age of 3 weeks, with a history of vomiting for one week. Clinical examination on admission was negative, but two days later it was noticed that the child was slightly jaundiced and that the stools were white. The total serum-bilirubin was 7·4 mg. per cent; free 3·7 mg. per cent and conjugated 3·7 mg. per cent. The urine contained bilirubin but no stercobilin. The child continued to vomit intermittently and the slight jaundice and the pale stools persisted; it was thought that she was probably suffering from neonatal hepatitis. Twenty-two days after admission the patient's abdomen was noted to be very distended, with evidence of free fluid, and there were fluid bulges in each inguinal region and at the umbilicus.

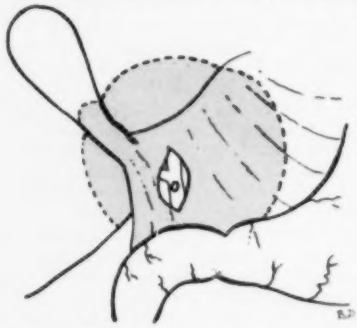

FIG. 611.—Diagram illustrating the duct perforation and the extent of the initial localized biliary accumulation as shown by the distribution of the bile-stained fibrin capsule.

At laparotomy on the following day the peritoneal cavity contained a large quantity of bile. When the right lobe of the liver was elevated, a deeply bile-stained, fibrin-lined cavity, bounded by the liver, the lesser omentum, and the pyloroduodenal region, was entered and dissection revealed a perforation of the anterior aspect of the common bile-duct just below the entrance of the cystic duct (*Fig.* 611). The perforation was roughly circular in outline, with necrotic margins, and occupied about one-third of the circumference of the duct. The biliary duct system was not dilated and a probe passed readily through the common duct into the duodenum. The perforation was sutured and cholecystostomy performed. A choledochogram, carried out through the cholecystostomy tube, one week after operation showed a normal duct outline and free entry of the dye into the duodenum (*Fig.* 612). The tube was removed on the tenth day after operation and the biliary fistula closed rapidly. When discharged from hospital ten days later the child was free from jaundice, was gaining weight, and the stools were of normal colour. One year later she remains well.

FIG. 612.—Choledochogram ten days after suture of the duct perforation. Normal outline of gall-bladder and ducts and free entry of the opaque medium into the duodenum.

Interrogation of the mother after operation revealed that the child's stools had been white since the onset of vomiting at the age of 2 weeks. It appears likely, therefore, that the duct perforated at this time, that the local accumulation of bile later led to jaundice by compressing the duct system, and that, some three to four weeks after

the beginning of symptoms, the localized biliary collection ruptured into the general peritoneal cavity.

DISCUSSION

It has been possible to find recorded in the literature 11 cases similar to the present one. Seven cases which were almost identical and in which the duct perforation was identified have been described by Caulfield (1936), Pettersson (1955) (4 cases), Talalak (1959) and Gertz (1959), while Caulfield (1936) and Davies and Elliot-Smith (1955) have reported 2 cases in which the clinical and pathological findings were the same except that no actual perforation could be recognized at operation. The 2 further cases were rather different. Byrne and Bottomley's (1953) patient had several pea-sized, bile-containing, cystic swellings, one of which had ruptured at the junction of the cystic duct with the common bile-duct. It is not clear, however, whether these were diverticula of the duct or small accumulations of escaped bile in the periductal tissues. Davies and Elliot-Smith's (1955) second case differs from the others in that the lower part of the common bile-duct, below the perforation, was atretic.

The pathogenesis of spontaneous perforation of the common bile-duct is not clear. In all cases in which the duct perforation was seen it was situated on the anterior wall near the entrance of the cystic duct. A developmental locus minoris resistentiæ may therefore have existed in this position and the presence of a developmental anomaly is supported by the coincidental findings, in Byrne and Bottomley's (1953) case of a solid gall-bladder and in Davies and Elliot-Smith's (1955) of an atretic common duct. The possibility that raised intraduct pressure is a prerequisite of ductal rupture is suggested by the case of the atretic duct and also by one of Caulfield's (1936) cases in which a slight stenosis was present in the lower part of the common duct. In none of the other recorded cases was there any anatomical abnormality of the bile-ducts, but in these obstruction by a mucus plug or by inspissated bile cannot be ruled out; the sequence of clinical events in the present case, however, does not suggest that ductal obstruction preceded the perforation. In one of Pettersson's (1955) cases there were small foci of fat necrosis in the vicinity of the perforation, suggesting that reflux of pancreatic secretions may be an aetiological factor.

The symptomatology in all cases of spontaneous bile-duct perforation has been very similar. The age of the child at the onset of symptoms has varied from 5 days to 5 weeks. Vomiting, pale stools, failure to thrive, and mild-to-moderate jaundice, the appearance of which was often later than that of the other symptoms, have been prominent complaints. Abdominal distension due to biliary ascites, often with inguinal and umbilical bulges, has been present in all cases except one of Pettersson's (1955), in which the bile tracked to form a localized swelling in the left side of the abdomen.

The infant tolerates remarkably well the presence of a large quantity of bile in the peritoneal cavity, and the prognosis in these cases is good even if surgical intervention is delayed, as it occasionally has been, for some weeks. Only 3 of the reported patients have died, 2 after operation, and 1, recognized at post-mortem examination, after nine weeks of non-surgical treatment. Closure of the perforation in the duct, with or without drainage of the biliary tract, has been performed in 4 cases. With the exception of one of Davies and Elliot-Smith's (1955) cases, in which choledochoduodenostomy was successfully performed because of duct atresia, the remainder have been treated by simple drainage to the site of biliary leakage.

It is interesting to speculate, as Caulfield (1936) did, on the possible association between spontaneous perforation of the common bile-duct in infancy and choledochal cyst appearing in later life. In none of the reported cases of duct perforation was the diagnosis made prior to the widespread intraperitoneal dissemination of bile, but in 8 cases it was apparent that the perforation had led, initially, to the formation, in the subhepatic pouch, of a fibrin-enclosed, localized accumulation of bile, and that this had then secondarily and subsequently ruptured into the general peritoneal cavity. It is conceivable that, if a balance were struck between leakage of bile from the duct and its re-entry from the fibrin sac, the latter might not rupture but, by organization of its wall, form a structure closely resembling the fully developed choledochal cyst which is seen in later childhood and in adult life.

SUMMARY

A case of spontaneous perforation of the common bile-duct in an infant is described. The pathogenesis, clinical features, and treatment of the condition and its possible relation to the choledochal cyst of later life are discussed.

I am indebted to Dr. F. P. Hudson for advice on the management of the patient and to Miss Barbara Duckworth for the drawing.

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DEVELOPMENTAL MESENTERIC CYSTS

By A. HARVARD BAKER, Scarborough

The opportunity of reporting 8 cases of mesenteric cyst occurring during a space of four years must be most unusual, since most writers on the subject agree that these cysts are very rare (Roller, 1935; Paul, 1948; Miller, 1954; Amos, 1959). Flynn (1930) considers that they are the rarest of all abdominal tumours and Warfield (1932) states that many surgeons in a full working life have never seen a case. Many surgical text-books ignore the condition altogether and contain no reference to these cysts.

The first reference to a mesenteric cyst appears to have been made in 1507 by Benevieni, a Florentine anatomist. Warfield (1932) collected 129 cases from the literature and added 2 personal reports. Rankin and Major (1932) found only 7 mesenteric cysts in the records of the Mayo Clinic, and Beahrs and Judd (1947), adding a case of their own, said that these 7 were the only such cases found in a million admissions to the Clinic. Thompson and Chambers (1946) estimated that the incidence was 1 in 100,000 admissions.

Some authors, however, suggest that the condition is not as rare as appears and they think that many cases are either not recognized or not reported (Flynn, 1930; Peterson, 1932; Warfield, 1932). This conclusion would appear to be supported by the present series as well as by Parsons (1936), who as long ago as 1936 collected 500 reports from the literature. Although many papers deal with single cases, larger series have been reported by Roller (1935) 3 cases; Handelsman and Ravitch (1954) and Peterson (1932) reported 5 cases each, and Gross (1953) in a very wide experience found 12 isolated mesenteric cysts and one multiple cystic condition of the mesentery.

AETIOLOGY

Higgins and Lloyd (1924) define mesenteric cysts as "cysts which occur in or near the mesentery, which are not dermoid or parasitic, and do not arise in a normally placed retroperitoneal organ", and this definition seems to be generally accepted. There are many difficulties in determining the exact origin of mesenteric cysts, and even careful microscopical examination does not always prove conclusive. Many cysts are thought to have migrated from their site of origin and gross anatomical relationships may be misleading. The microscopical appearances are often altered by the growth of the cyst and the pressure exerted by the contents on the wall, and many of these cysts have undergone various vicissitudes and accidents before they are removed, with the production of the changes of acute or chronic inflammation, hæmorrhage, necrosis, or degeneration. Three criteria will be discussed—the contents, the lining, and the wall.

The Contents.—This varies enormously and may be serous, opalescent, milky or 'chylous', hæmorrhagic, gelatinous, fibrinous, or frankly infected by bowel organisms (Roller, 1935). In polycystic conditions the picture may be further complicated by the fact that different loculi may contain different types of contents (Amos, 1959; MacNab and Menzies, 1950; Parsons, 1936), some having serous and some chylous or hæmorrhagic fluid. The presence of milky fluid has been held by many authors to constitute proof positive of a lymphatic origin, and Gross (1953) suggests that there are islets of misplaced lymphatic tissue without drainage vessels and that these become cystic. Certainly many cases have been described which seem to be analogous with cystic hygroma of the neck and which present as a polycystic, multiloculated tumour of the mesentery (MacNab and Menzies, 1950; Steel, 1933; Walker and Cooper, 1959). Other authors, notably Dowd (1900), Niosi (1907), and Higgins and Lloyd (1924), strongly express the view that the presence of 'chyle' is a secondary phenomenon and is due to the permeation of chyle from the rich network of mesenteric lacteals into a preformed cyst, often of retroperitoneal origin. Milroy Paul (1948) has reported a case in which the microscopical picture gives unequivocal evidence that the cyst is of enterogenous origin and yet the contents were chylous. Although this case seems to be unique, it must raise doubts whether all cysts with 'chylous' contents are of lymphatic origin. It is difficult to accept that lymphatic tissue itself secretes milky fluid, which is thought to be formed in the intestinal papillæ and merely conveyed through the lymphatic channels. Nevertheless, in the absence of histological proof to the contrary, these milk-containing cysts must occasionally be classified as of the lymphatic type.

The Lining Epithelium.—Like the contents, the lining epithelium is very variable. The presence of stratified epithelium with hair follicles and sweat glands, as in the case reported by Penberthy and Brownson (1938), makes it clear that the cyst is a true dermoid. In developmental cysts the lining may be a more or less faithful replica of the intestinal mucosa with columnar epithelium and glandular crypts (Paul, 1948). In other cysts the epithelium may be columnar, cuboidal, flattened, or entirely absent, in which last case the cyst is lined by areolar or fibrous tissue. A definite endothelial lining suggests either a lymphatic or a mesocolic origin, but in one case reported here the lining varied, being columnar in places and flattened in others. It seems clear that the increase of pressure in the cyst, due either to the gradual increase in the contents or to the sudden increase in tension from torsion or hæmorrhage, may grossly modify or completely destroy the lining cells.

The Wall.—Again, this is variable and subject to changes from the accidents and incidents to which these cysts are liable. A well-defined smooth muscle layer may be present, especially in cysts of enterogenous origin, but much more frequently scattered bundles of smooth muscles are found. Such smooth muscle-bundles are often found in the walls of cystic hygroma and in angiomata. The wall of many cysts shows only areolar tissue, and when this is a thin layer the cyst may be semitranslucent, but when the

wall is thicker much fibrous tissue may be present. There may be honey-combed spaces, suggesting a lymphatic origin and various cellular patterns, with collections of lymphocytes or the products of inflammation. The presence of lymphocytes has been held to indicate a lymphatic origin, but this appearance could be consistent with a degenerating tuberculous node or with the reaction of the surrounding tissues to what has become, in effect, a foreign body. When congestion, hæmorrhage, or infection has supervened, these conditions are reflected in the microscopical appearances of the cyst wall. Occasionally calcification occurs, but this seems to be rare. It is described by Vaughn, Lees, and Henry (1948).

PATHOLOGY

In gross appearance mesenteric cysts vary widely. They may be small or large; single or multiple; thick-walled or thin; tense or flaccid. An excellent account of their characteristics is given by Grimes (1949). They are found at any age and have been reported in the fœtus. The youngest patient reported by Gross (1953) was only three days old and he found 5 cases in children under 7 months. In the series analysed by Burnett, Rosemond, and Bucher (1950), 74 patients were aged 20 or under, while 114 patients were over 20 years. The older age groups are not in any way exempt and 5 of the 8 cases included in this report were over 20 years old. The commonest site for these cysts was found to be in the mesentery of the small intestine, 46 per cent according to Burnett and others (1950), but cysts have been described in most of the mesenteric sites in the abdomen.

Various classifications have been made (Dowd, 1900; Niosi, 1907; Warfield, 1932; Ewing, 1940), but that of Illingworth and Dick (1956) is both simple and comprehensive. They list the varieties of mesenteric cyst as:—

1. Traumatic.—Cysts formed in hæmatomata or around a foreign body; e.g. a swab—as described by Denkin.
2. Inflammatory.—Especially tuberculous nodes with cystic degeneration.
3. Parasitic.—Hydatid.
4. Neoplastic.—Degeneration of malignant tumours.
5. Dermoid and teratoma.
6. Developmental: (*a*) Lymphatic; (*b*) Enterogenous; (*c*) Mesocolic; (*d*) Urogenital.

Only the last main category will be further considered in this paper and examples will be given of three of these four varieties.

CYSTS OF LYMPHATIC ORIGIN

Included under this heading are two main pathological conditions, multiple lymphangiomatous formations and simple cysts, the contents of which may be serous, chylous, or hæmorrhagic. There have been several recent descriptions of the lymphangiomatous type of cyst, and articles by Amos (1959), MacNab and Menzies (1950), and Walker and Cooper (1959) have been published recently. The appearances are of a polycystic condition, often very extensive and difficult to eradicate by resection. Microscopically they strongly resemble cystic hygroma of the neck and they appear to be of undoubted lymphatic origin.

The simple cysts, which may be multiple but discrete, and which vary much in size, shape, and contents, are of much more debatable origin. Some of those classified under this heading may in fact be of urogenital origin, but their histology is so indefinite that, for convenience and because they correspond to previous cases described as lymphatic, they are included in this section. Three cases appear to be of this nature.

Case 1.—J. T., male aged 56 years, presented at the Out-patient Department on Dec. 17, 1958. He had gastrectomy for peptic ulcer in 1946. In 1957 he developed

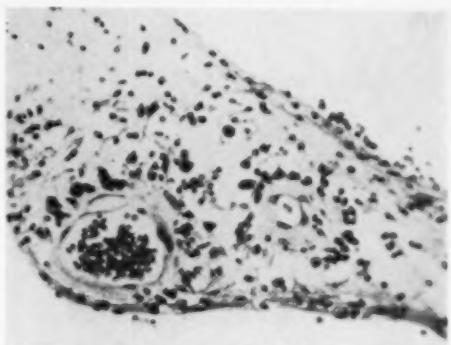

FIG. 613.—*Case* 1. Microphotograph showing angiomatous spaces. (× 168.)

mild diabetes, which was controlled by diet, and in 1956 he was diagnosed as having pernicious anæmia, which was treated by cytamen. In spite of these complaints his condition was very good and he was now suffering from hæmorrhoids of many years' duration, which occasionally bled. Examination showed a mobile mass in the abdomen above and to the left of the umbilicus. This was thought to be a carcinoma of the colon.

INVESTIGATIONS.—Blood-count 100 per cent. No glycosuria.

Barium enema (Dec. 22—Dr. H. F. March): "No lesion of the colon apart from a few diverticula. The mass seems to be well below the left side of the transverse colon and nearer the lower part of the descending colon, but does not seem to have any connexion with the large bowel."

AT OPERATION (Jan. 2, 1959).—A cyst was present in the root of the mesentery of the small intestine at its upper part, near the origin of the superior mesenteric vessels. There were a few adhesions and it was enucleated without undue difficulty and without any damage to the vessels.

PATHOLOGY (Dr. K. Froome).—"The tumour is 5 cm. in diameter and is partly solid and partly cystic. The cystic portion contains gelatinous material. Histologically, the cyst wall is composed of dense fibrous tissue containing angiomatous formations. In some areas old hæmorrhage is seen and much hæmosiderin in the phagocytes. The appearances suggest that the cyst is of developmental origin." (*Fig.* 613.)

Case 2.—J. S., female aged 17 years, was seen as an out-patient on Dec. 21, 1955, complaining of central abdominal pain of an aching nature for six months and an abdominal lump in the right iliac fossa, which has appeared and disappeared several times. There has been some frequency of micturition hourly during the day and twice during the night. Examination showed a fat girl with a prominent abdomen and a reniform tumour on the right side.

INVESTIGATION.—No abnormality was found in the urine. Intravenous pyelogram showed a normal right kidney, but a space-occupying tumour was shown in the bony pelvis (*Fig.* 614). When she was seen again on Jan. 9, 1956, the tumour was larger and operation was advised.

FIG. 614.—*Case* 2. Radiograph showing the outline of the cyst in the pelvis.

AT OPERATION (Feb. 3, Mr. L. S. Debenham).—There was a huge mesenteric cyst, with two smaller ones adjacent. Later an almost equally large cyst was found higher in the mesentery, again with two adjacent smaller cysts. All these were dissected out of the mesentery without damage to the blood-supply of the bowel. During dissection one of the smaller cysts burst, liberating some milky white fluid.

PATHOLOGY (Dr. K. Froome).—"The specimen consists of two large cysts, measuring approximately 20 cm. in diameter. The cysts are bilocular, containing milky fluid together with a few pieces of sebaceous-like matter. Three multilocular smaller cysts measuring 4 cm. in diameter are present. Histologically the appearances are those of lymphatic cyst of the mesentery. The wall is composed of loose fibrous tissue. These lesions are congenital in type, comparable with cystic hygroma of the neck." (*Fig.* 615.)

Case 3.—M. B., female aged 12 years, presented at Out-patient Department on April 29, 1955, with a history that for about 6 weeks she had attacks of abdominal pain, worse after meals and sometimes causing vomiting. Her appetite was poor and she had lost weight. She looked ill and was admitted for investigation.

INVESTIGATION.—Blood-count: Hb 108 per cent, W.B.C.s 4200, of which 37 per cent were lymphocytes. Mantoux test—1–10,000 strongly positive. Radiography: Barium meal suggested a duodenal ulcer. Fractional test-meal showed a rather high acid curve.

PROGRESS.—Treated with magnesium trisilicate with diet-improvement.

Jan. 20, 1956: Continues well and is putting on weight.

Feb. 17: Radiograph showed persistent pylorospasm and a niche, probably due to ulcer.

April 19, 1957: Admitted as an emergency with acute abdominal pain and vomiting. The pain is severe and continuous. Slightly distended, rather fat abdomen, no rigidity, but some tenderness in the epigastric and periumbilical regions. Liver dullness present.

Radiograph showed no evidence of pneumoperitoneum, but leaking perforation was suspected and conservative treatment was given. Her condition remained satisfactory until April 23, when she was obviously much worse and operation was decided on.

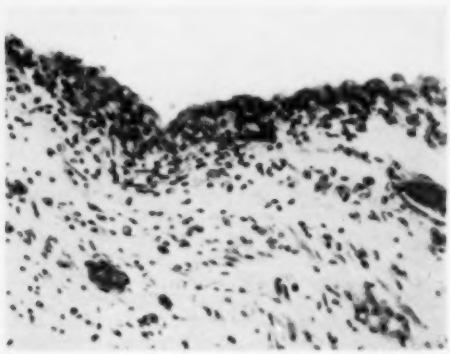

FIG. 615.—*Case* 2. Photomicrograph showing endothelial lining. (× 168.)

AT OPERATION.—At laparotomy a large part of the small intestine was black and gangrenous, owing to a volvulus through almost three complete circles. At the apex of the volvulus was an enormous mesenteric cyst, containing creamy fluid. The gangrenous area of bowel was resected with end-to-end anastomosis.

Post-operatively her condition improved, but she started to deteriorate on April 28 and died later that day.

PATHOLOGY (Dr. K. Froome).—"The specimen consists of a large thin-walled mesenteric cyst, which shows no special features, lying adjacent to small intestine. The cyst wall is lined by a single layer of flattened epithelium. It is extremely congested and the adjacent gut is intensely engorged and necrotic in places. The cyst is of developmental origin and almost certainly lymphatic, since it contains chyle."

CYSTS OF ENTEROGENOUS ORIGIN

As the name implies, these cysts have a wall the structure of which closely mimics that of the intestine, with a columnar-cell lining, glandular crypts, and well-defined smooth-muscle layers. Gross (1953) thinks that these are one variant of duplication of the intestine and states that the blood-supply is the same as that of the adjacent bowel and that the cyst cannot be enucleated without damaging this blood-supply, so that resection with the corresponding portion of the gut is always necessary. The vestigial remains of the vitello-intestinal duct have been suggested as a probable origin of this type, but reference is also made by Warfield (1932) and by Higgins and Lloyd (1924) to the work of Lewis and Thyng (1908), who found downgrowths of displaced intestinal tissue in the mesentery of embryos of man, rabbit, and pig. It is suggested that though these normally fail to develop, on occasion these remnants may produce the

enterogenous type of cyst. Reference has already been made to the case reported by Paul (1948) in which the wall was typical of an enterogenous origin, but the contained fluid was chylous. These cysts may retain a connexion, often a solid stalk, with the adjacent bowel, and 2 such cases are reported by Grimes (1949), while Handelsman and Ravitch (1954) report a very large cyst of this type which measured about 32 cm. in diameter.

No cyst of proved enterogenous origin has been met in this series.

CYSTS OF MESOCOLIC ORIGIN

These cysts are of completely different aetiology and the suggestion is made that they are formed by failure of the adjacent layers of peritoneum to coalesce during the stages of fœtal rotation of the intestines, especially the third stage. They appear to be relatively common in cases which show malrotation of the bowel, and 4 cases are described by Bentley and O'Donnell (1959).

In all these cases malrotation was associated. Since the wall is formed from the peritoneum itself, the most usual histological finding is an endothelial lining and a thin wall of areolar tissue, but pressure changes and accidents can of course alter these findings. Two cases which appear to be of this type are included in this series.

Case 4.—O. J., female aged 41 years, was seen on July 27, 1959. She had for two years suffered from attacks of pain in the right iliac fossa, sometimes severe enough to cause vomiting. There were no urinary symptoms and examination showed marked tenderness over the right iliac fossa. A pathological appendix was suspected.

AT OPERATION (Sept. 3).—Through a right paramedian incision the abdomen was explored. The appendix contained fæcoliths and was removed. A peritoneal cyst, about the size of a lemon, was found in the right paracolic groove about the level of the middle of the ascending colon. The cyst shelled out easily and proved to have no connexion with the bowel or with any retroperitoneal organ. No abnormality was found in the pelvis or elsewhere in the abdomen (*Fig.* 616).

PATHOLOGY (Dr. K. Froome).—"The cyst is lined by a single layer of columnar epithelium which in places has become flattened. The wall is composed of loose fibrous tissue. 90 c.c. of opalescent fluid were present." (*Figs.* 617, 618.)

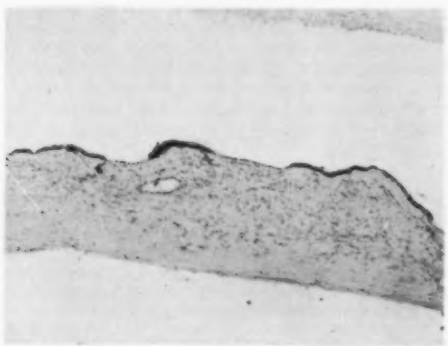

FIG. 617.—*Case* 4. Photomicrograph showing lining of columnar cells, flattened in places. (× 24.)

Case 5.—L. N. R., male aged 58 years. At operation for gastric ulcer on June 26, 1959 (Mr. T. F. R. Griffin), two semitransparent cysts were found, hanging from the free border of the ligamentum teres of the liver. They were of 1 cm. and 1½ cm. diameter and were removed.

PATHOLOGY (Dr. K. Froome).—"The cyst was thin-walled and contained watery fluid. The cyst is of developmental origin and is lined with a single layer of flattened epithelium."

Both these two cysts occurred at places where fusion of peritoneum takes place, but *Case* 4 bears some resemblance to the type of parovarian cyst which is thought to occur in remnants of the Wolffian body, and which are considered under the heading of cysts of urogenital origin. It may well be that this case ought to be placed in that category.

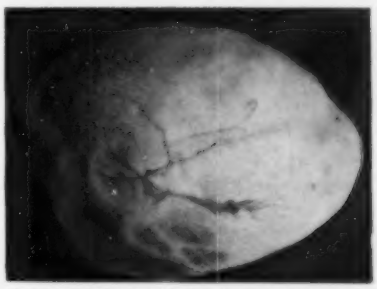

FIG. 616.—*Case* 4. Showing the cyst after removal.

FIG. 618.—*Case* 4. Photomicrograph showing high-power view of lining cells. (× 168.)

CYSTS OF UROGENITAL ORIGIN

These cysts are thought to arise in rudiments of the mesonephros or other sequestrations from the developing urogenital system. In fœtal life the urogenital fold, containing the mesonephros or Wolffian body, projects into the cœlomic cavity on either side of the primitive dorsal mesentery. At one stage it has a mesentery of its own, which disappears early in fœtal life. Although most of the Wolffian body disappears, remnants remain, mainly in the broad ligaments of the uterus, which are thought to lead on occasions to the formation of parovarian cysts. It is postulated that other remnants may at times migrate into the mesentery and form the focus from which some mesenteric cysts develop.

Dowd (1900) described a cyst which was indistinguishable from a pseudo-mucinous cyst of the ovary, situated between the stomach and the transverse colon. It was apposed to the pancreas between the layers of the transverse mesocolon, but was not growing from the pancreas. He also quoted cases reported by Macdonald, Morton, Lohlein, Bantock, and Carter, all of which he thought were of undoubted

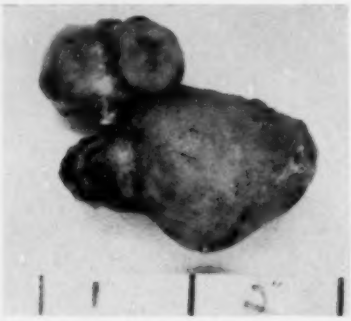

FIG. 619.—*Case* 6. Photograph of multilocular cyst after removal.

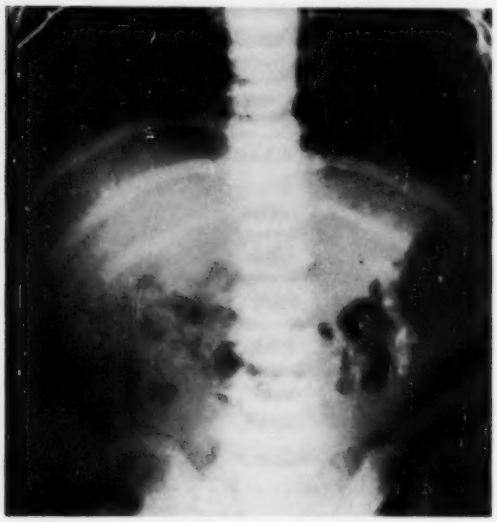

FIG. 621.—*Case* 6. Subcutaneous pyelogram, showing excretion of dye from left side and absence of secretion from right kidney.

urogenital origin. Niosi (1907), describing a case, quotes the cases described by Dowd, Macdonald, and Frenzel, and strongly supports Dowd's championship of a urogenital origin for many mesenteric cysts. Niosi's own case appears to have been unique and it showed a very mixed histological picture. In addition to areas resembling intestinal mucosa, there are histological elements resembling uriniferous tubules and suprarenal tissues and a small area which seems to be a chorionepithelioma. Although he classes it as a mesenteric cyst, it would appear to fit better into the category of teratoma. Higgins and Lloyd (1924) also reject the theory of a lymphatic origin for most mesenteric cysts and support the theory of an origin either from urogenital sequestrations or from isolation of intestinal diverticula during fœtal development, as described by Lewis and Thyng (1908).

Three cases of this series appear to be of probable urogenital origin, and there is some doubt as to

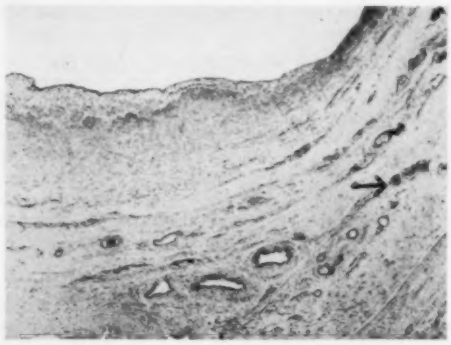

FIG. 620.—*Case* 6. Photomicrograph showing scattered renal tubular structures and a glomerulus (arrow). (× 18.)

whether *Case* 4 should not also be included here. One case reported seems to be unique and wide search of the literature has failed to disclose any similar reported case. Most writers give little prominence to the possibility of a urogenital origin, and the position is expressed by Paul (1948) when he says that histological proof is rarely forthcoming to support the theory. The case reported here gives ample proof, not only of urogenital origin, but also that urogenital structures may migrate to occupy a position in the mesentery itself.

Case 6.—P. R. F., male aged 7 weeks, was admitted on Jan. 26, 1959. He had been uncomfortable after his feed at 6.30 a.m. and refused the feed at 10 a.m. He vomited at about 11 a.m. and vomiting persisted at half-hourly intervals; the vomit consisted of small amounts of watery fluid. He was fed at 2 p.m. but vomited the milk at 2.15 p.m. and again at 4.30 p.m. At 5.30 p.m. he began to wail, and screamed several times at intervals, and the continuing vomiting produced streaks of blood. At this stage he was admitted to hospital and at 6.30 p.m. he passed blood and mucus per rectum. On examination, he was obviously in distress and he had a tense strangulated right inguinal hernia.

Abdominal examination disclosed a hard palpable mass in the epigastric region. It was thought that he had a double pathology, strangulated hernia being associated with an intussusception.

AT OPERATION.—Herniotomy disclosed a strangulated right inguinal hernia, which contained viable but extremely congested small intestine. The contents were reduced, the neck ligated, and the sac excised. After reduction, re-examination of the abdomen showed that the palpable mass was still present and laparotomy through a right rectus incision was undertaken. There was a polycystic mass near the root of the mesentery of the small intestine and between the mesenteric layers. It was dissected out and proved to be quite separate from the intestine. No damage was inflicted to the blood-supply of the bowel. The cyst seemed to be self-contained and no structure resembling ureter needed division. A slow intravenous

infusion was given, and convalescence was uneventful (*Fig.* 619).

PATHOLOGY (Dr. K. Froome).—"Histologically, this multilocular cyst is of renal origin and no doubt it is of developmental type. It is lined by a single layer of flattened epithelium. Kidney tissue is present in the wall of the cyst and comprises glomeruli and tubules, some of the latter containing albuminous casts." (*Fig.* 620.)

RADIOGRAPHY (March 12—Dr. H. F. March).—"Subcutaneous pyelogram. Excretion is visible from the left kidney and the left pyelogram appears normal, but there is no visible excretion from the right side up to 40 minutes." (*Fig.* 621.)

Case 7.—J. R., female aged 33 years, was admitted on June 15, 1959, complaining of pain in the right iliac fossa of three days' duration. The pain started in the

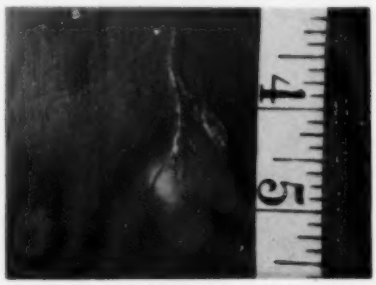

FIG. 622.—*Case* 7. Photograph of cyst after removal.

right iliac fossa and was continuous with superadded spells of colic. There had been no nausea or vomiting, but her appetite was poor. The bowels were regular, and there was no dysuria or frequency and no history of previous abdominal trouble. On examination her general condition was good, the tongue clean and moist. There was slight tenderness in the right iliac fossa; rectal examination was negative. Bowel-sounds were noted as present. Temperature 98·8°; pulse 96. The condition appeared to be a settling appendicitis.

AT OPERATION (June 17).—The appendix was adherent and appendicectomy was performed. A soft, thin-walled cyst was found behind the cæcum and mesentery of the terminal ileum. It was dissected out without difficulty (*Fig.* 622). *No right ovary was present.*

PATHOLOGY (Dr. K. Froome).—"A thin-walled cyst containing clear fluid. The cyst is quite benign and is lined by a single flattened layer of epithelium. ? developmental in origin." (*Fig.* 623.)

Case 8.—A. B., female aged 65 years, was admitted on Nov. 21, 1957, with a large abdominal swelling. She stated that her abdomen had been swollen since childhood. She complained of a dragging pain on walking and over the last year she had lost over 4 st. in weight and had been subject to frequent attacks of vomiting.

Examination showed a large cystic swelling in the left upper quadrant of the abdomen, passing under the left ribs and almost fixed, although there was slight movement on respiration. There was no connexion with the pelvis or pelvic organs.

AT OPERATION (Nov. 22).—Left paramedian incision. A large globular swelling was found, situated in the transverse mesocolon, and presenting below the colon and passing back to the region of the pancreas. It was very vascular and many large vessels coursed over it, but enucleation was successfully undertaken (*Fig.* 624).

No damage occurred to the blood-supply of the transverse colon. The cyst was anatomically adjacent to the pancreas, but did not appear to arise from it. However, in the course of securing the large blood-vessels a small tear was noticed in the pancreas, and the tail of the gland was resected with the cyst, although it showed no obvious abnormality.

PATHOLOGY (Dr. K. Froome).—"A cyst measuring about 19 cm. in diameter and weighing 120 g. It is thin-walled and contains altered blood. The thin wall of the cyst is simply composed of dense fibrous tissue. Blood-clot adheres to the inner surface. It is possible that this cyst is of developmental origin. The pancreas shows no special features."

These three cases all seem to qualify as cysts of urogenital origin, since *Case* 6 presents histological proof which is indisputable; *Case* 7 has absence of one ovary and a cyst of developmental type, and *Case* 8 has a cyst which closely resembles in many respects

FIG. 623.—*Case* 7. Photomicrograph showing a single layer of living cells. (× 168.)

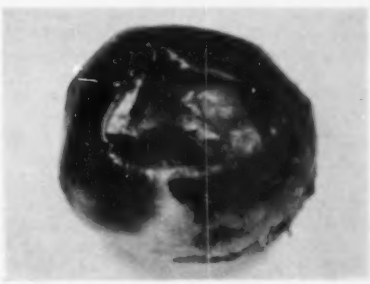

FIG. 624.—*Case* 8. Large cyst from transverse mesocolon, probably of urogenital origin.

the case originally described by Dowd (1900), although the histological appearances have been grossly modified by the effects of recurrent hæmorrhages into the cyst which were the probable cause of the patient's symptoms.

SYMPTOMATOLOGY AND DIAGNOSIS

One of the astonishing features of these cysts is that they may grow to a very large size without producing anything serious in the way of symptoms. In many cases, slight discomfort and the feeling of an abdominal mass are the only presenting symptoms, and it should be noted that even a large cyst may not be felt either because it is well cushioned by the intestines or by the fat of the abdominal wall, or that the cyst is not tense enough to make itself felt.

Radiographs are sometimes useful, but here again a very large cyst may not give any characteristic radiological picture, as is exemplified by *Case* 3 in this series. Only rarely is the cyst directly visible on radiography, as in *Case* 2 of this series (*see Fig.* 614).

There are, however, a large number of complications to which these cysts are liable and a percentage of them present as acute abdominal emergencies, especially as cases of intestinal obstruction. The complications which have been described are:—

1. Intestinal obstruction due to adhesions, kinking (Steel, 1933); volvulus (*Case* 3, also Handelsman and Ravitch, 1954); torsion of a pedicled cyst (Parsons, 1936).
2. Rupture (Miller, 1954).
3. Cyst impacted in the pelvis (Paul, 1948).
4. Acute infection of a loculus with fæcal contents (Roller, 1935).
5. Malignant degeneration is mentioned by Peterson (1932).
6. Calcification is mentioned by Vaughn and others (1948).

Blood in the stools is mentioned by Miller (1954) and by Paul (1948) and also occurred in *Case* 6 in this series. Although the occurrence of these cysts is not very common, the condition should be borne in mind when investigation of a lump proves to be negative for the more usual causes.

TREATMENT

The ideal treatment of these cysts appears to be enucleation of the cyst, without damage to the blood-supply of the bowel. This is not always possible, and in such cases resection and anastomosis of the bowel may be essential. According to Gross (1953), this will always be the case with cysts of enterogenous origin, and it may apply to many cases with complicating intestinal obstruction or multiple cystic conditions enveloping the intestine. In most of the cases encountered it has proved surprisingly easy to enucleate the cyst, provided that no attempt is made to hurry the procedure. Except in *Case* 8, bleeding has been slight and the cyst has proved to be relatively avascular. Aspiration of the cyst is insufficient in itself and should only be undertaken as a prelude to dissection. In a very occasional case marsupialization has been successful, but this should only be undertaken if there is no prospect of enucleation.

SUMMARY

1. Eight cases of the comparatively rare condition of mesenteric cysts have been encountered during the space of four years.

2. Because cysts are often featureless, there is great difficulty in proving the origin of some of them.

3. One case was found which appears to be unique in that there was unmistakable evidence of its origin in the renal anlage. A further case is described in which a cyst was present and the right ovary was absent, and yet a third case is described which appears to be of urogenital origin.

4. It is strongly suggested that many mesenteric cysts, even when they contain 'chylous' fluid, are not necessarily lymphatic in origin, but may be urogenital or enterogenous cysts which have secondarily acquired this milky fluid by perfusion from the lacteals in the mesentery.

Acknowledgements.—My thanks are due to my colleagues, Mr. L. S. Debenham for permission to include *Case* 2 and Mr. T. F. R. Griffin for permission to include *Case* 5. I should also like to thank Dr. K. Froome for his great help with the pathology and photomicrographs; Dr. H. F. March for his X-ray reports; Dr. Peter Whitehead for his help in the translation of the article by Niosi; Mr. T. W. Dryden and Mr. H. Bennett for help with photographs.

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PRIMARY LYMPHOSARCOMA OF THE THYROID

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PRIMARY lymphosarcoma of the thyroid is nowadays considered to be a rare disease. Up to 1906, primary sarcoma was diagnosed almost as commonly in the thyroid as primary carcinoma, but Graham (1925) believed that a very high percentage of cases reported as sarcoma were typical examples of malignant adenoma. Ewing (1940) went further, doubting whether primary sarcoma of the thyroid had ever been satisfactorily demonstrated. Kellett and Sutherland (1949), however, reported 5 cases, in none of which was the histology suggestive of carcinoma; these they regarded as examples of primary reticulosarcoma. They noted the presence of lymphoid hyperplasia in the tumour-free thyroid tissue, and after considering the possibility that these tumours arose in struma lymphomatosa, concluded that they more probably developed in the lymphoid hyperplasia so often found in the thyroids of elderly females. Ten such cases reported by Brewer and Orr (1953) were associated with two sharply differing types of clinical course, 6 patients dying within a few months and the others remaining alive for relatively long periods. The examples of unexpectedly long survival, and an association with similar tumours in the gastro-intestinal tract, led Brewer and Orr to postulate some unusual type of granulomatous reaction with a predilection for the thyroid and the intestinal wall. Since no histological distinction could be made between the rapidly-fatal cases and those which ran a benign course, they suggested that the term 'struma reticulosa' be used until more data became available.

Although there have been several later reports, much uncertainty still attends the prognosis, the relationship to struma lymphomatosa, and the significance of the gastro-intestinal lesions. We therefore present a further 5 cases, and a possible sixth, of primary lymphosarcoma of the thyroid, occurring in Manchester Royal Infirmary in the period 1951–59. The term 'lymphosarcoma' is used here in the sense employed by Winston Evans (1956) to include tumours of lymphocytic, lymphoblastic, and reticulum-cell types, or a combination of these types.

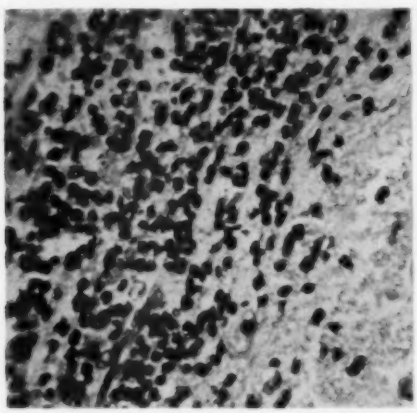

FIG. 625.—*Case* 1. Pleomorphic tumour, partly necrotic, in the left lobe of the thyroid. H. and E. (× 340.)

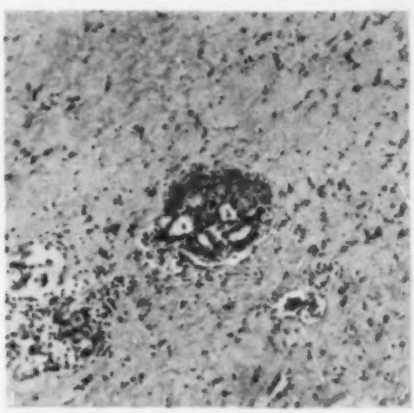

FIG. 626.—*Case* 1. The fibrotic right lobe, showing small islets of metaplastic and oxyphilic epithelium, and lymphocytic infiltration of the fibrous tissue. H. and E. (× 105.)

CASE REPORTS

Case 1.*—A 76-year-old married woman was admitted as an emergency to the medical wards in December, 1951. She had been confined to bed for five weeks with weakness, loss of weight, and some vomiting, but no obvious bleeding and no pain. Twice during the preceding 2½ years she had attended the medical out-patient clinic on account of osteo-arthritis; on neither occasion had any thyroid abnormality been noted. She was found to be extremely pale and weak, with an imperceptible pulse and a barely recordable blood-pressure. The hæmoglobin concentration was 4·9 g. per cent and the total and differential white-cell counts were normal. Physical examination revealed no enlargement of the liver, spleen, or thyroid.

The diagnosis was severe anæmia and cachexia, probably due to undetected malignancy. Following blood transfusion her general condition improved. Five days after admission a clinical diagnosis of myxœdema was made, and administration of thyroid extract was begun. Two days later she developed early gangrene of the left foot, due to arterial and venous thrombosis; her condition deteriorated rapidly, she vomited foul black material, and she died on the ninth day after admission.

PATHOLOGY.—At necropsy the principal abnormalities were in the thyroid, the small intestine, and the lungs. The left lobe of the thyroid was occupied by a nodule 3 cm. in diameter, of rubbery consistency, composed of

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* This case was briefly referred to by Brewer and Orr (1953) as a personal communication from Professor A. C. P. Campbell.

a firm margin and a necrotic centre. The right lobe was very small and fibrotic. In the small intestine there were four ulcers, each 2–3 cm. long and each entirely encircling the bowel wall. Perforation of one of the ulcers was associated with organizing peritonitis. The lungs were œdematous, with patchy consolidation in the lower lobes. There were several infarcts in the lower lobes; emboli in the smaller branches of the pulmonary artery had arisen from thrombosis of the femoral and calf veins. There was no evidence of tumour tissue in any site other than the thyroid and intestine.

Microscopically, the nodule in the left lobe of the thyroid was a reticulum-cell sarcoma (*Fig.* 625); the greater part of the tumour was necrotic, only a narrow peripheral zone surviving. The tumour was pleomorphic, the nuclei of the cells ranging from small and deep-staining to large and vesicular, with occasional very large cells with elongated or indented nuclei; multinucleate cells were not seen. Silver impregnation revealed a delicate reticulin network, enclosing small groups of cells. The capsule of the mass was infiltrated by small lymphocytes only. The right lobe of the thyroid was largely replaced by dense fibrous tissue; the scanty parenchymatous islets were composed of oxyphilic or squamous epithelium, and were infiltrated by lymphocytes and plasma cells. The appearances were those associated with myxœdema, differing from the usual picture only in the presence of lymphocytes throughout the fibrous tissue as well as in the parenchymatous islets (*Fig.* 626).

Sections from the intestinal ulcers showed replacement of almost the entire intestinal wall by tumour tissue identical in appearance with that seen in the left lobe of the thyroid.

Diagnosis: Reticulum-cell sarcoma of thyroid and small intestine; myxœdema.

Case 2.—A 54-year-old married woman was admitted to the medical wards in April, 1954, with allergic purpura. She was found to have a firm, mobile swelling occupying the right lateral lobe of the thyroid gland, which had appeared suddenly twelve months before and had not changed in size since. There was no dysphagia or dysphonia. The serum-proteins and cholesterol were normal.

She was readmitted in July, 1955, complaining of increasing swelling of her neck with, in addition, a feeling of constriction and some dysphagia. Examination revealed diffuse thyroid enlargement, more marked on the right side, and radiography of the neck showed tracheal compression. The serum-cholesterol and B.M.R. were both normal.

At operation the thyroid was pale and nodular, with marked bilateral retrosternal extensions. It was considered to be a lymphadenoid goitre and the isthmus was removed with subtotal resection of the right lateral lobe and partial resection of the left lobe.

One month after discharge from hospital, swelling recurred in the lower part of the neck, and shortly afterwards her left arm began to swell. On readmission five months after operation there was massive enlargement of the lower neck from the left supraclavicular fossa to the submandibular area, made up largely of the deep cervical lymph-nodes; in addition there was an enlarged left axillary node. The left arm was swollen and dilated veins were visible on the chest wall. Repeated total and differential white-cell counts were normal. She was referred to the Christie Hospital for irradiation, and received regional X-ray therapy to her neck with a maximal skin dose of 500 r. A full blood-count at this time was again normal. Liver function tests were also normal; the plasma-protein estimations were albumin 3·4 g. per cent and globulin 3·4 g. per cent. Electrophoresis of the plasma-proteins showed that there was no separation into α-2 and β-globulin fractions, otherwise the electrophoretic pattern showed no abnormality. The mass in the neck almost disappeared following irradiation.

As the patient lived in Nottinghamshire a postal follow-up only was obtained. Three months after X-ray treatment her own doctor reported a small residual lump, 2·5 cm. in diameter, under the left sternomastoid. There was no sign of metastases. Again five months later there was no sign of metastases and the residual lump in the neck was smaller. She was, however, still troubled by purpura and in addition had developed pernicious anæmia. She died at home in June, 1957, eighteen months after irradiation, the certified cause of death being pernicious anæmia and purpura. She thus lived for four years after the first appearance of the thyroid swelling, and according to her own doctor there was no definite evidence of recurrence at the time of her death. Necropsy was not performed.

PATHOLOGY.—The specimen comprised the greater parts of both lateral lobes, together weighing 210 g. The capsule was smooth and thin. The cut surface was pale and resembled pancreas in texture.

Microscopically, the gland was divided by narrow bands of connective tissue into islets of varying size. In two of the five sections examined, and in part of a third, the islets were very heavily infiltrated by lymphocytes and plasma cells, with a few ill-defined lymphoid follicles. The little recognizable thyroid tissue consisted of isolated small acini, composed of oxyphilic epithelium and devoid of colloid, sparsely scattered through the mass of infiltrating cells. Apart from the unusual degree of parenchymal replacement by infiltrating cells, there was nothing to distinguish the picture from one of chronic thyroiditis.

In the remaining areas, where there was an equal degree of replacement, the infiltrating cells were of a different character. The majority were much larger than lymphocytes, with large round, elongated or polygonal nuclei, some vesicular, some hyperchromatic, with occasional mitotic figures. The appearances were those of a reticulum-cell sarcoma.

The capsule was infiltrated by mature lymphocytes and a few plasma cells; tumour cells could not be identified here.

Diagnosis: Reticulum-cell sarcoma, arising in chronic non-specific thyroiditis.

Case 3.—A 49-year-old married woman was admitted to the surgical wards in October, 1955, for removal of an adenomatous goitre. She complained of a choking sensation for thirteen months before admission and had noted a goitrous swelling three months later. Examination revealed what appeared to be a simple adenomatous goitre affecting principally the isthmus and right lateral lobe. The hæmoglobin concentration was 11·8 g. per cent; the white-cell count was normal, with a normal differential count. At operation the whole gland was found to be hard and nodular, with a pale avascular appearance. No normal thyroid tissue appeared to be present and the lesion was considered to be malignant. A total thyroidectomy was performed.

Nearly three years later there was marked sensitivity of the whole of her neck, especially around the scar. There was no sign of recurrence in the neck, and examination of the abdomen revealed no abnormality.

Four years after operation she was still in good general health. There were no abdominal symptoms or signs. Her neck was still tender on the left side, where there was a soft swelling 3 cm. in diameter, which was considered more likely to be regenerated thyroid tissue than an enlarged lymph-node. It was decided to watch this a little longer before taking any action. Serum-cholesterol, plasma-proteins, and liver function tests at that time were normal.

The tanned red-cell hæmagglutination test for thyroid auto-antibodies, performed for the first time on this occasion, was positive to a titre of 1–160.

PATHOLOGY.—The specimen was composed of both lateral lobes and the isthmus, total weight 32 g. On

section the gland was seen to be composed of solid yellowish-grey nodules up to 2 cm. in diameter.

Microscopically, the gland was traversed by broad and narrow bands of connective tissue (*Fig.* 627). The islets of tissue thus formed were densely infiltrated by lymphocytes, in some areas showing an ill-defined follicular arrangement, and by larger more immature cells, including reticulum cells. Mitotic figures were most numerous in, but were not confined to, the germinal centres of lymphoid follicles. Argyrophil fibres were scanty throughout the tumour.

In contrast, the cells infiltrating the collagenous bands and the thyroid capsule were in no way suggestive of

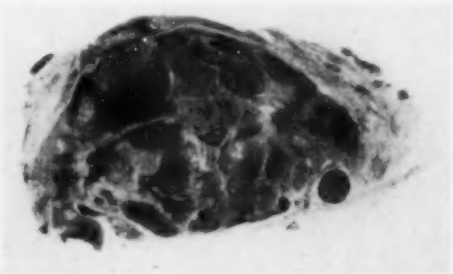

FIG. 627.—*Case* 3. Tumour tissue intersected by bands of fibrous tissue. H. and E. (× 3.)

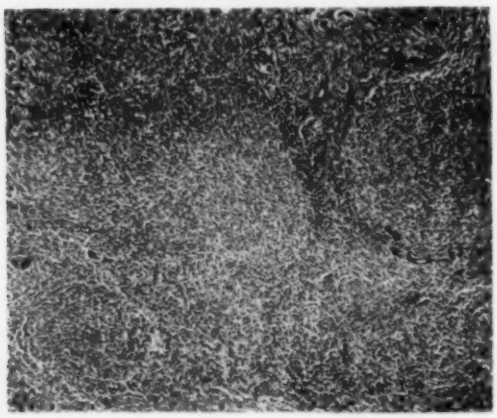

FIG. 629.—*Case* 4. Giant follicular lymphoma. A few thyroid acini can be seen within the tumour tissue. H. and E. (× 40.)

malignancy, consisting of small lymphocytes and plasma cells only.

Within the tumour tissue there were a very few small thyroid acini, lined by oxyphilic epithelium. There were also several islets of hyperplastic thyroid tissue, each occupying two or three low-power fields, sharply demarcated from the tumour tissue and not infiltrated by neoplastic or inflammatory cells (*Fig.* 628).

Diagnosis: Lymphosarcoma arising in chronic non-specific thyroiditis.

Case 4.—A man aged 47 years was admitted to the surgical wards in November, 1956, with a provisional diagnosis of carcinoma of the thyroid. For two months previously he had noted loss of energy, a little loss of weight, and a swelling in his neck. On examination, there was a rather hard but mobile swelling of the left lobe of the thyroid. The basal metabolic rate was increased by 25 per cent; uptake of radioactive iodine was 24 per cent at two hours; serum-cholesterol, plasma-proteins, liver function tests, and a full blood-count were normal. A radiograph of his chest showed no metastases, but some deviation of the trachea to the right. He had had no abdominal symptoms, and fæcal occult blood examinations were negative.

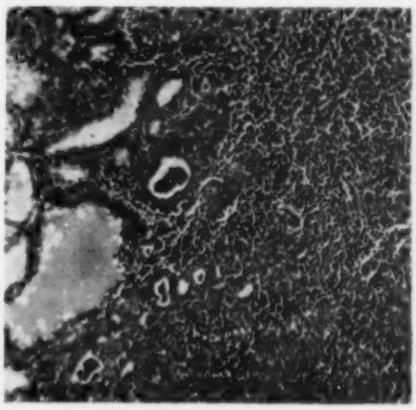

FIG. 628.—*Case* 3. Higher-power view of the tumour, and part of an islet of epithelial hyperplasia. H. and E. (× 105.)

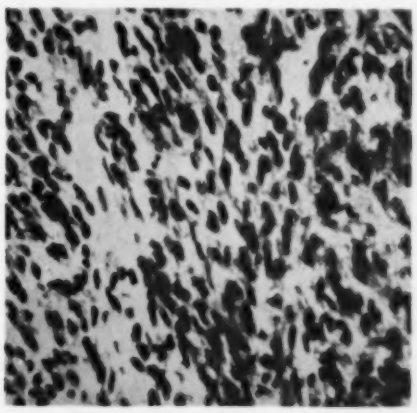

FIG. 630.—*Case* 4. Metastasis in liver, secondary to tumour of stomach. H. and E. (× 350.)

At operation the appearances suggested malignancy of the left lobe of the thyroid, while the right lobe appeared normal; the left lobe was totally excised.

He was re-examined at three-monthly intervals and remained symptom-free until eighteen months after operation, when he complained of central abdominal pain on taking food, and some weight loss. There was no sign of any recurrence in the neck, and no abnormality in the abdomen apart from epigastric tenderness. Barium-meal X-ray examination suggested a lesion in the upper part of the stomach distorting the fundus. He was re-admitted, and at operation in July, 1958, a large mass was found involving the posterior wall of the cardiac end of the stomach. There were large, fleshy, purplish lymph-nodes in the gastrosplenic omentum, and multiple metastases in both lobes of the liver. A biopsy of one of the liver nodules was taken and the abdomen closed.

Ten months later he was obviously deteriorating rapidly, with marked loss of weight and œdema of all four limbs, and the abdominal masses were much bigger. He died shortly afterwards at home nearly three years after the onset of symptoms. Necropsy was not performed.

PATHOLOGY.—The enlarged left lobe of thyroid weighed 133 g., and consisted throughout of homogeneous pinkish-grey tissue, showing vague trabeculation but otherwise resembling lymphoid tissue.

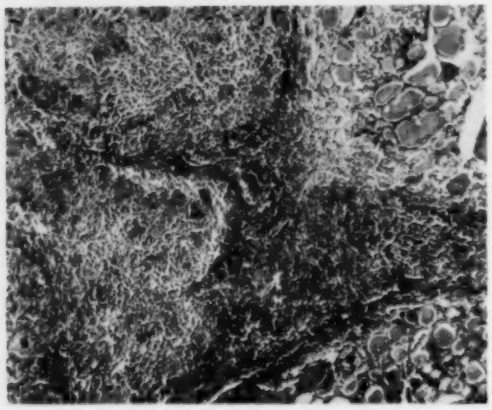

FIG. 631.—*Case* 5. The margin of the tumour, showing infiltration of thyroid tissue. The follicular structure of the tumour was well defined in this section. H. and E. (× 56.)

Microscopically, fibrosis was present, but did not approach the degree seen in the preceding two cases. There was very extensive replacement of the thyroid parenchyma, which was reduced to scanty small foci of oxyphilic or squamous epithelium, by lymphocytes and lymphoblasts. In some areas these cells were grouped to form irregular giant follicles, which often appeared to be coalescing (*Fig.* 629), while in other areas there was uniform infiltration by lymphoblasts, without discernible follicular arrangement. Silver impregnation confirmed the follicular arrangement, showing numerous argyrophil fibres at the periphery of the follicles but few or none in the germinal centres. The capsule of the gland was infiltrated by small lymphocytes only.

The fragment of liver showed a malignant tumour of different appearance. It was composed of densely-packed large spindle cells with hyperchromatic nuclei (*Fig.* 630); mitotic figures were numerous. There were many cytoplasmic vacuoles, which did not stain with either the mucicarmine or periodic acid-Schiff methods. The tumour cells tended in some areas to form distinct bundles, but elsewhere there was no detectable arrangement.

Diagnosis: Giant follicular lymphoma of thyroid, arising in chronic non-specific thyroiditis. Metastatic tumour in liver, which might be either sarcoma or carcinoma.

Case 5.—A spinster, aged 55 years, was admitted to the surgical wards in January, 1959, with a twelve-month history of swelling in the neck and a nine-month history of hoarseness and nocturnal choking sensation. She had been taking thyroid extract for fourteen years to keep her weight down. Examination revealed a large multinodular goitre more marked on the right side. A radiograph of her chest was normal apart from some tracheal narrowing above the thoracic inlet. A full blood-count was normal.

At operation a large, rather avascular, multinodular goitre with bilateral retrosternal extensions was found, and a subtotal excision of both lateral lobes and isthmus was performed.

Four months later she was very well; she was again putting on weight in spite of dieting and so thyroid medication was started again. There was no sign of any recurrence in the neck and she had no abdominal symptoms or signs.

Ten months after operation she was still well and gaining weight. There were no other symptoms or signs of myxœdema. No abnormality was found on examination

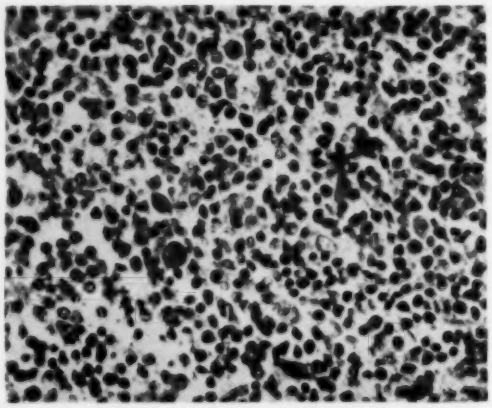

FIG. 632.—*Case* 5. High-power view of a non-follicular area, showing the different types of cells composing the tumour. H. and E. (× 350.)

of neck or abdomen. The serum-proteins and liver function tests were found to be normal, but the serum-cholesterol was 465 mg. per cent. The tanned red-cell hæmagglutination test for thyroid auto-antibodies, which had not been previously performed, was positive to a titre of 1–1280.

PATHOLOGY.—The specimen comprised the greater parts of both lateral lobes, together weighing 115 g. The right lobe was composed largely of solid, pale grey tumour tissue, homogeneous centrally but mottled peripherally, imperfectly demarcated from apparently normal thyroid tissue. The left lobe was composed of multiple, encapsulated colloid nodules of varying size, some showing recent hæmorrhage.

Microscopically, the tumour in different areas showed two different types of structure. One was clearly follicular, composed of lymphocytes and lymphoblasts forming well-defined giant follicles, sharply demarcated from the normal thyroid tissue in some areas, but infiltrating it in others (*Fig.* 631). The other type was diffuse, composed of lymphocytes, lymphoblasts, and reticulum cells, and a few binucleate cells (*Fig.* 632); mitotic figures averaged 1 per high-power field. There was a rich reticulin network, enclosing small groups of cells.

The capsule of the thyroid was infiltrated by cells similar to those of the tumour.

Throughout the tumour, there were very scanty islets of epithelium, some of oxyphilic type, some in the form of acini containing macrophages.

The left lobe had the multinodular structure of 'adenomatous goitre'. The thyroid tissue between the nodules was abnormal in that it showed fibrosis, some focal infiltration by lymphocytes and plasma cells, mild epithelial hyperplasia, and a few foci of oxyphilic epithelium.

Diagnosis: Giant follicular lymphoma and reticulum-cell sarcoma, arising in non-toxic nodular goitre with focal thyroiditis.

A further case has been seen in which, although the thyroid was never examined microscopically, the available evidence favours a diagnosis of primary lymphosarcoma of the thyroid:—

Case 6.—A 53-year-old married woman had noted a slowly enlarging goitrous swelling for over twenty years. For six weeks before her admission to the medical wards in October, 1953, she had noted a rapidly increasing left-sided swelling of her neck, and for two weeks had complained of a productive cough. She had no pressure symptoms. Examination revealed a marked firm enlargement of the left lobe of the thyroid with a lesser enlargement of the right lobe and, in addition, one large firm lymph-node in the left supraclavicular fossa. Radiography of her chest was normal. Her hæmoglobin concentration was 12·7 g. per cent; the white cells numbered 12,700 per c.mm., with a normal differential count. Both vocal cords were mobile. A clinical diagnosis of carcinoma of the thyroid was made. A biopsy excision of the left supra-clavicular lymph-node was performed and the patient transferred to the Christie Hospital for radiotherapy.

In November, 1953, she received a nineteen-day course of X-ray therapy to the neck, the total tumour dose being 2500 r. The swelling in her neck completely disappeared. She remained well for four months, when she complained of a cough, and radiographs of her chest showed metastases at both lung bases. At that time examination of her neck revealed no abnormality. She was readmitted to the Christie Hospital for chest baths, after which she was never well enough to attend for follow-up, and she died in May, 1954, less than twelve months after the onset of her symptoms. Necropsy was not performed.

PATHOLOGY.—Microscopically, the excised node was replaced by a uniform sheet of cells showing no suggestion of acinar grouping. The cells were of variable size, the larger ones resembling reticulum cells, the others lymphoblasts and lymphocytes. Mitotic figures were numerous. Argyrophil fibres were relatively scanty, and showed no tendency to enclose groups of cells.

Diagnosis: Carcinoma cannot be certainly excluded, but the appearances more strongly suggest an immature type of lymphosarcoma.

DISCUSSION

The clinical features of the six cases are summarized in *Table I*.

The 4 cases in which the diagnosis was made on a thyroidectomy specimen all occurred within the period 1955–59. During this five-year period, 896 surgical thyroid specimens were examined in the Department of Pathology, including 17 cases of carcinoma and 28 cases of diffuse chronic thyroiditis. Welch, Chesky, and Hellwig (1958) found 4 cases in a total of 215 malignant thyroid tumours and saw 202 cases of lymphadenoid goitre during the same period.

Age and Sex Incidence.—The average age of our cases was 55·8 years; 5 of the 6 patients were females. Combining the five largest series (Kellett and Sutherland, 1949; Dinsmore, Dempsey, and Hazard, 1949; Brewer and Orr, 1953; Lindsay and Dailey, 1955; Walt, Woolner, and Black, 1957b), the age range is 30 to 81, with an average of 59·5 years. There were 43 cases in females and 9 in males, a ratio of nearly 5 to 1, but with the inclusion of the many smaller series the ratio falls to 4 to 1.

Symptoms and Signs.—The principal symptom is the rapid enlargement of a firm or hard swelling in the neck, with, or more usually without, a history of pre-existing goitre. The swelling is usually accompanied by pressure symptoms, such as a sense of constriction in the neck, difficulty in swallowing, or hoarseness. There may be weakness and loss of weight. Recurrent nerve paralysis and obvious fixation of the swelling are not common findings.

Welch and others (1958) considered that a clinical history of rapid onset of thyroid enlargement, coupled with symptoms of dysphagia, dyspnœa, weakness, weight loss, and hoarseness, are consistent enough to constitute a syndrome; but such an association of symptoms would not seem to justify a pre-operative diagnosis of lymphosarcoma, as they could equally well be due to carcinoma, or even to thyroiditis. Though pressure symptoms are commonly reported, and occurred in all but one of our cases, they were noted in only 5 out of 21 cases by Walt and others (1957b).

Fairly sudden enlargement of the thyroid in a post-menopausal woman should arouse suspicion, but unless there is infiltration of the surrounding structures malignancy is not easily diagnosed before operation. Rapid enlargement occurring in a gland already known to be affected by struma lymphomatosa would suggest malignancy; Pollock and Sprong (1958) believed the incidence of malignancy (carcinoma as well as sarcoma) in struma lymphomatosa to be 10 per cent or even higher.

Operative Findings.—Most commonly the gland at operation has an irregular nodularity and is pale and relatively avascular. It is firm and friable, and its cut surface is uniformly greyish-white, though sometimes with pale yellow nodules. Many glands have been indistinguishable from struma lymphomatosa at operation. Infiltration of the overlying

Table I.—CLINICAL FEATURES

CASE	AGE	SEX	DURATION OF GOITRE	CLINICAL DIAGNOSIS	TREATMENT	SURVIVAL AFTER TREATMENT
1	76	F.	No goitre	Malignant cachexia	None	—
2	55	F.	2 yr.	Struma lymphomatosa	Partial thyroidectomy. Irradiation for recurrence	Died after 2 yr. from unrelated causes
3	49	F.	10 mth.	Non-toxic nodular goitre	Total thyroidectomy	Alive without recurrence 4½ yr. later
4	47	M.	2 mth.	Carcinoma of thyroid	Total lobectomy	Died 2½ yr. later of malignant gastric tumour
5	55	F.	12 mth.	Non-toxic nodular goitre	Subtotal thyroidectomy	Alive without recurrence 12 mth. later
6	53	F.	Over 20 yr.	Carcinoma of thyroid	Irradiation	Died 6 mth. later with disseminated tumour

strap or sternomastoid muscles, deep fascia, and carotid sheath has been reported several times, but was not noted in any of our cases.

Microscopical Diagnosis.—Malignant lymphoid tumours of all types have been reported as arising in the thyroid, ranging from mature lymphocytic type of lymphosarcoma to reticulum-cell sarcoma. The microscopical features are the same as seen in similar tumours arising in other sites. There have also been reports of primary Hodgkin's disease in the thyroid, though without adequate confirmation (Cohen and Moore, 1954; Smithers, 1959), and 1 case of primary plasmocytoma (Shaw and Smith, 1940).

The present series includes no tumours of mature lymphocytic type; 2 were of intermediate type, 2 immature, and in 2 there was formation of giant lymphoid follicles. The latter structure was reported in 1 case by Kenyon and Ackerman (1955).

The two principal conditions with which primary lymphosarcoma of the thyroid might be confused are small-cell carcinoma and chronic thyroiditis.

When, as in our *Cases* 1 and 5, there is a small-cell tumour confined to one part of the gland, the differential diagnosis is from carcinoma, which, in the absence of clinical evidence of a carcinoma in any other site, may be considered primary. Criteria for the differentiation of the two conditions were discussed by Dinsmore and others (1949), Scott (1952), and Walt, Woolner, and Black (1957a). Often, as in our *Case* 6, the response to radiation may assist in differentiating sarcoma from carcinoma, but there may remain some cases in which, even after necropsy, a final diagnosis cannot be made. In *Cases* 4 and 5 the arrangement of the neoplastic tissue into giant follicles left no doubt as to the lymphoid origin of the tumour. In the other cases the intermingling of small and large cells resembling lymphocytes and reticulum cells, the lack of even a rudimentary acinar arrangement, and the nature of the reticulin pattern, all supported the diagnosis of lymphosarcoma.

The problem of differentiating primary lymphoma from chronic thyroiditis was lightly dismissed by Warren and Meissner (1953) and Welch and others (1958), but the occasional coexistence of these conditions may give rise to considerable difficulty in the interpretation of the microscopical picture. The tumours in *Cases* 2, 3, and 4 of this series were apparently associated with chronic thyroiditis; in *Case* 3, two of the five sections examined showed non-neoplastic lymphocytic and plasma-cell infiltration, and had these areas alone been examined the diagnosis would have been one of chronic non-specific thyroiditis. In 3 cases of Walt and others (1957b), the initial histological diagnosis of chronic thyroiditis was belied by subsequent events; the diagnosis was changed to malignant lymphoma in 2 cases after review of the slides, and in the 1 case only after further sampling of the tissue.

The most useful criteria for the recognition of malignancy in this type of case would seem to be the degree of parenchymal replacement by infiltrating cells, the type of infiltrating cell, the number of mitotic figures, evidence of capsular invasion, and perhaps the presence or absence of epithelial changes.

Very intense infiltration by inflammatory cells may occur in chronic thyroiditis, but areas of complete replacement of the parenchyma should arouse suspicion of malignancy. Reliance cannot always be placed on the type of infiltrating cell, as the picture in a mature lymphocytic type of lymphosarcoma might be indistinguishable from the lymphocytic infiltration of chronic thyroiditis, but the absence of lymphoid follicles and plasma cells from one area in a gland which otherwise shows these features might point to a diagnosis of sarcoma, while the presence of large immature reticulum cells would be conclusive. The number of mitotic figures is also a useful guide, providing that mitosis occurring in the germinal centres of lymphoid follicles is left out of account. Brewer and Orr (1953) found microscopical fields in cases of thyroiditis which were qualitatively similar to reticulosarcoma, and thought that the diagnosis of reticulosarcoma must at least to some extent be determined on quantitative grounds. Our experience, however, supports the view of Kellett and Sutherland (1949) that in thyroiditis such fields are limited to the centres of follicles, and the follicular structure is not destroyed.

Invasion of the capsule of the gland, or of striated muscle outside the gland, is of course conclusive of malignancy, provided that the infiltrating cells are similar in type to those infiltrating the thyroid. In 4 of our cases capsular infiltration by plasma cells and mature lymphocytes could be contrasted with parenchymal infiltration by more immature cells, without plasma cells. Brewer and Orr (1953) noted that infiltration of voluntary muscles by the fibrolymphoid reaction was often in advance of the spread of the apparent tumour tissue. It might also be noted that such infiltration outside the gland, seen most notably in Riedel's struma, may also occur to a lesser degree in other forms of chronic thyroiditis.

The epithelial changes in these tumours have been those usually associated with chronic thyroiditis—namely, small acini, empty or containing macrophages, oxyphilic epithelium, and occasional foci of squamous metaplasia. The total absence of any such changes in the uninvolved portion of the thyroid is rare and might suggest that the gland is secondarily involved by a lymphoid tumour arising elsewhere.

Relationship to Preceding Thyroid Disease.—Three of our cases appear to have arisen in diffuse chronic thyroiditis, 1 in myxœdema, and 1 in focal thyroiditis associated with adenomatous goitre; in the remaining case there was a preceding goitre the histological structure of which is not known. The diagnosis of preceding diffuse thyroiditis in 3 cases is supported by the presence of the characteristic epithelial changes; invasion of the thyroid by malignant lymphoid tissue originating either in the gland or in adjacent lymph-nodes does not itself cause such changes (Lindsay and Dailey, 1955). The degree of fibrosis, too, cannot be attributed to the presence of the tumour and indicates a pre-existing thyroiditis. On histological grounds, Lindsay and Dailey accepted 7 of their 8 cases as arising in struma lymphomatosa, although only 1 case had a history of preceding goitre. It is noteworthy that in the latter, and in a few similar cases (our *Case* 3; Case 1 of Kenyon and Ackerman, 1955; Case 2 of Winship and Greene, 1955; Case 4 of Welch and others, 1958), the clinical history of preceding goitre has been paralleled by a histological picture of diffuse chronic thyroiditis with only localized malignant change. A case is

mentioned by Smithers (1959) in which Hashimoto's disease was diagnosed on the first operation specimen, while a recurrence of goitre eighteen months later was found to be due to lymphosarcoma.

While there is thus often clinical or pathological evidence of preceding struma lymphomatosa, there are other cases in which the tumour appears to have arisen in the symptomless focal thyroiditis so often found in the thyroids of post-menopausal females (Kellett and Sutherland, 1949). There has also been a case of lymphosarcoma arising in goitrous hypothyroidism (Adé, 1941), and our *Case* 1 is an example of sarcoma arising in classical myxœdema.

The one factor common to all these antecedent diseases of the thyroid is lymphocytic infiltration or hyperplasia. It would seem that lymphosarcoma may arise in a thyroid which is the seat of lymphoid hyperplasia from whatever cause. As all such conditions are most commonly found in post-menopausal females, this view is in keeping with the age and sex incidence of primary lymphosarcoma of the thyroid; the predominance of females, and the average age of about 60, provide a contrast with the incidence of lymphosarcoma elsewhere, which occurs more commonly in males and more often in a younger age group.

The Association with Gastro-intestinal Tumours.—This association has been observed too often to have occurred by chance. In our *Case* 1 the gastro-intestinal tract was the only site of tumour tissue outside the thyroid, as in cases reported by Dick and Kellett (1951), Brewer and Orr (1953), and McKenzie, Moore, and Fidler (1958). The case reported by Canney (1956) may well have been another example; thyroidectomy for reticulosarcoma was followed two years later by gastrectomy for a similar tumour, and the patient was alive and well two years after the second operation.

Records of 14 necropsies, including our *Case* 1, were summarized by Walt and others (1957b), who gave post-mortem findings on 5 of their own cases; adding to these the reports of Massini (1956), Welch and others (1958), and McKenzie and others (1958), records of 24 necropsies are now available. Out of 16 cases in which there was distant dissemination of the tumour, there are 14 examples of gastro-intestinal tract involvement, the only exceptions being Case 2 of Massini (1956) and Case 3 of Walt and others (1957b).

It need not be assumed that the gastro-intestinal tumours are in all cases secondary to the primary thyroid tumour. Such selective deposition of metastatic tumour at so distant a site, without any explanation in terms of vascular or lymphatic distribution, would be a very unusual circumstance. Metastatic tumours are uncommon in the gastro-intestinal tract, and Willis (1952) noted that they are accompanied almost invariably by blood-borne secondary growths in other organs. In his own series of 500 necropsies on malignant disease, Willis found only 2 cases in which there were both gastric and intestinal metastases; these were secondary to carcinomas of the thyroid and pharynx.

The alternative explanation would be the multifocal origin of the tumour. Such multifocal origin of lymphosarcoma within the gastro-intestinal tract is, of course, not uncommon, and it may be that the thyroid is sometimes the initial site of origin in gastro-intestinal lymphosarcomatosis. A recent post-mortem study of 300 generalized lymphoid tumours (Naylor, 1959) indicates that involvement of the thyroid is commoner in females, and suggests that the thyroid is in some cases a site not of metastases but of multifocal origin.

In our *Case* 4 death was due to an undifferentiated tumour of the stomach, histologically dissimilar to the thyroid tumour which had previously been excised. An awareness of the likelihood of associated gastro-intestinal tumour had led to a deliberate search for such lesions both during the first admission and at subsequent three-monthly examinations, until the presence of a tumour in the stomach was discovered nineteen months after thyroidectomy. Since proof of the sarcomatous nature of the gastric tumour is lacking we can only record this occurrence without drawing deductions as to its significance.

Prognosis.—The natural course of the disease cannot be accurately known, as the number of reported cases is small, many are poorly documented, and they differ as regards histological type and the nature of treatment. Moreover, there must remain some doubt as to whether all the cases were indeed sarcomas, and were indeed primary in the thyroid; opportunities for post-mortem confirmation of the diagnosis have been remarkably few.

Although in most cases death has occurred within a few months of operation, there have been occasional examples of survival for many years. Extensive involvement of the neck structures carries a very poor prognosis, but among the reported cases of long survival are several in which the tumour had infiltrated the thyroid capsule. A correlation between survival and the histological maturity of the tumour was found by Walt and others (1957b), but no such correlation could be detected by Lindsay and Dailey (1955). The type of chronic thyroiditis in which the lymphocytic infiltration is of such unusual degree as to mimic lymphosarcoma was regarded by Woolner, McConahey, and Beahrs (1959) as probably benign; one of their cases showed no histological change when a recurrent goitre was removed ten years after the original thyroidectomy.

Brewer and Orr (1953) were sufficiently impressed with the variations in survival to suggest that a single histological appearance might be associated with two sharply differing types of clinical behaviour. Of their 10 cases, 6 died within a short time of operation, the longest survival being 8 months. The remaining 4 patients were alive and well 16, 10, 9, and 2 years later. These examples of survival were considered to exclude the likelihood of malignant neoplasia, and led Brewer and Orr to postulate an unusual type of granulomatous reaction with a predilection for the thyroid and the intestinal wall.

While lymphosarcoma has in general a poor prognosis, its course is known to be unpredictable and not too closely related to histological type. The majority of patients die within a short period, while a few, especially in the older age groups, survive for many years (Lumb, 1954). Survival seems to depend less on the histological type than on whether or not the tumour is localized at the time of treatment (Paterson, Tod, and Russell, 1950). Primary lymphosarcoma of the intestine, to which primary lymphosarcoma

of the thyroid may be related, similarly has a high mortality, but similarly with a minority of patients surviving for long periods (McSwain and Beal, 1944; Spellberg and Zivin, 1949; Irvine and Johnstone, 1955). In primary lymphosarcoma of the stomach, too, the pattern of survival is similar; Stout (1953) reported 4 out of 35 patients remaining well over periods ranging from 10 to 19 years, and Marshall and Adamson (1959) reported 4 out of 21 patients alive and well 10 years or more after operation. Stout concluded that there are two biological types of lymphosarcoma—a slowly progressive, relatively benign type; and the common variety, with a more rapid progress to a fatal termination.

The same would seem to be true of lymphosarcoma of the thyroid.

'Struma Reticulosa'.—This term was introduced by Brewer and Orr (1953) to describe a histological picture which appeared to be associated with two sharply differing types of clinical course. It was intended only as an interim designation, to be used until criteria became available for the differentiation of the benign from the malignant type. Now that more cases are on record, it is becoming clear that 'struma reticulosa' has the same significance as primary lymphoid or reticulo-endothelial tumours in other organs; there is now little reason to believe that the classical histological picture of lymphosarcoma as seen elsewhere carries any different implications when it occurs in the thyroid.

It might therefore be as well to discard the term 'struma reticulosa', especially as it fails to convey the highly malignant nature of many of the cases, and substitute a diagnosis of lymphosarcoma or reticulum-cell sarcoma.

Treatment.—When the diagnosis of sarcoma of the thyroid is suspected clinically or at operation, the most logical form of treatment is radical excision in the hope that the lesion, as may often be the case, is confined to the thyroid. In cases where radical excision is technically impossible, the patient should be referred for radiotherapy after adequate biopsy.

As the diagnosis is often not evident at operation, the surgeon may be faced with the problem of what action to take when an apparently benign goitre is reported by the pathologist as lymphosarcoma or 'struma reticulosa'. The possibility of thyroid involvement as part of a generalized lymphosarcoma must first be eliminated. The question of X-ray therapy will then arise; there is not at present sufficient evidence available to show whether it is better to withhold radiation until there is evidence of recurrence, or whether, as advocated by Walt and others (1957a, b), post-operative radiotherapy should be employed in every case.

Careful follow-up at frequent intervals is essential. One should not be misled by the apparently benign sound of the term 'struma reticulosa' into regarding it as a variant of struma lymphomatosa. At follow-up the abdomen as well as the neck should be examined and specific inquiry should be made concerning abdominal symptoms. Local recurrences in the neck after surgery are probably best treated by irradiation. Gastric or intestinal tumours should be treated surgically on their own merits. There is evidently a special liability for these gastro-intestinal lesions to perforate.

SUMMARY

Five cases of primary lymphosarcoma of the thyroid, and a possible sixth, are reported, and the literature is reviewed.

This tumour arises in glands which are the site of lymphoid hyperplasia of different degrees, ranging from the mild focal thyroiditis commonly found in the thyroid of post-menopausal females to established struma lymphomatosa.

In nearly all cases in which there has been distant dissemination of the tumour, the gastro-intestinal tract has been involved. It is probable that the gastro-intestinal lesions are new tumours rather than metastases from the thyroid.

The prognosis is generally poor, but a minority of patients survive for long periods.

'Struma reticulosa' is considered to have the same significance as lymphosarcoma arising in other sites.

Acknowledgements.—We are grateful to the physicians and surgeons of Manchester Royal Infirmary for permission to use their records; to Professor A. C. P. Campbell and Mr. H. T. Simmons for criticism of the manuscript; to Dr. G. Taylor for the thyroid auto-antibody estimations; and to Mr. N. Mowat for the photomicrographs.

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MALIGNANT MELANOMA WITH MELANOSIS AND MELANURIA, AND WITH PIGMENTED MONOCYTES AND TUMOUR CELLS IN THE BLOOD

AUTORADIOGRAPHIC DEMONSTRATION OF TYROSINASE IN MALIGNANT CELLS FROM PERITONEAL FLUID

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MELANOSIS is the name given to the condition of abnormal deposition of melanin in the tissues. Although darkening of the skin and mucous membranes occurs in other conditions, melanosis involving most of the organs of the body is seen only as a rare complication of malignant melanoma. In such cases the skin may become a dark grey or slate colour (see the illustrations of Wickham Legg, 1884; Trueblood, 1947; Albeaux-Fernet, Laumonier, and Collart, 1949; and Fitzpatrick, Montgomery, and Lerner, 1954) and melanuria is characteristic.

CASE HISTORY

The patient (Reg. No. 255563), a lady aged 33 years, was first admitted to the Churchill Hospital, Oxford, in April, 1958. She had had a pigmented mole on the left side of the abdomen since birth, but this had changed in colour from dark brown to slate blue, and increased in size from 1 cm. to 7 cm. diameter in the course of 3 years. For 4 months she had noticed a dull ache in the lower abdomen and the appearance of numerous slate-blue spots over her body. One month before admission she started to vomit occasionally, and was found to have a mass in the abdomen. A biopsy of a subcutaneous nodule was taken at the Newbury District Hospital (Mr. J. Joyce) and showed a metastasis of malignant melanoma.

On examination at the time of admission, she was found to be an ill-looking woman, well covered, with a dark complexion. Her conjunctivæ were coloured brown, and there were numerous palpable and visible blue nodules scattered over the whole body.

There was a large pigmented nævus 7 cm. in diameter below and to the left of the umbilicus and a healed biopsy scar in the right iliac fossa. Round this scar was an area of brown pigmentation, the site of extravasation of blood at the time of the biopsy. There was a large irregular mass arising out of the pelvis, and the liver was enlarged and irregular.

Her urine was dark on passing, turning darker on standing, and gave the chemical tests for melanin precursors.

Palliative treatment was obviously all that could be contemplated. She was given chlorpromazine, analgesics, and hydrocortisone, and on this régime she made a remarkable symptomatic improvement, so much so that although on admission she was regarded as approaching a terminal phase, she became well enough to be discharged home ten days later.

Soon after discharge she stopped taking these drugs and her pain and vomiting returned, of sufficient severity to demand further admission. Palliative therapy was again started, and she made a slow, though quite definite, recovery, leaving hospital one month later.

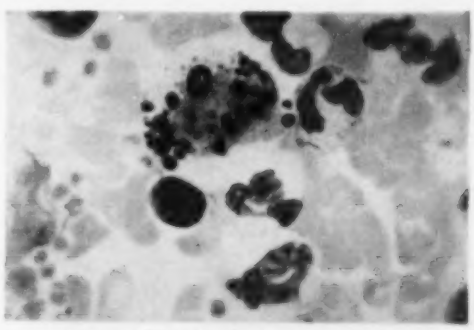

FIG. 633.—Microscopical field from a white-cell concentrate of blood, showing a macrophage containing melanin. May-Grünwald-Giemsa. (× 1000.)

On one further occasion she stopped cortisone for a short period, with rapid return of symptoms, but on starting it again, considering the widespread nature of the disease, she maintained a remarkably satisfactory condition for a further four months. There was, however, little or no change in the palpable secondary deposits, and her skin pigmentation increased slowly, so that she became dusky grey in colour.

In November, 1958, her abdominal pain and distension increased rapidly, and her condition deteriorated. She was readmitted, and 27 pints of blood-stained ascitic fluid were aspirated, but she died twelve days later.

LABORATORY INVESTIGATIONS.—

The *urine* was brown when passed, and darkened still further on standing. The supernatant gave the chemical reactions of melanin precursors. The deposit consisted of brown amorphous material, with some pigment-laden phagocytic cells.

The *hæmatological findings* on admission were as follows:—

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Hæmoglobin 63 per cent (9·3 g. per cent). White-cell count 5800 per c.mm. Concentrated films of white cells, made with the object of searching for tumour cells, showed numerous monocytes containing small pigment granules, and smaller numbers of phagocytic cells heavily laden with pigment in masses of varying size (*Fig.* 633). The monocytes also frequently showed clear vacuoles.

The pigment was pale yellowish-brown in unstained films, dark blue with May-Grünwald-Giemsa (as shown in *Figs.* 633–635), and brownish-black with Fontana's ammoniacal silver nitrate. Schmorl's reaction revealed minute blue granules in a higher proportion of monocytes than were shown in the May-Grünwald-Giemsa films. The pigment was slowly bleached by hydrogen peroxide (30 vol. per cent).

Marrow obtained by sternal puncture (Dr. L. G. Lajtha) showed the same pigment in the marrow fragments, both free and inside reticulum cells and macrophages.

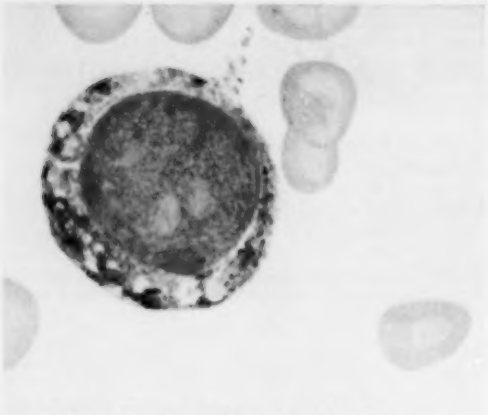

FIG. 634.—A tumour cell found in a white-cell concentrate of peripheral blood. Numerous small grains of melanin are present in the cytoplasm. May-Grünwald-Giemsa. (× 1500.)

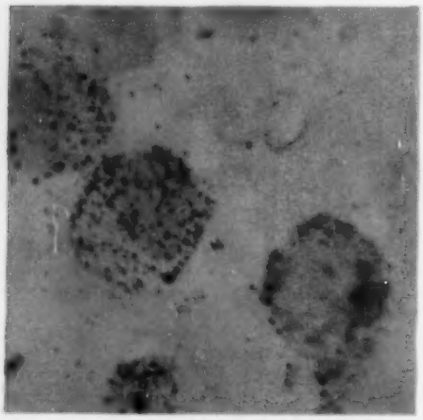

FIG. 636.—Autoradiograph of peritoneal fluid deposit after application of ^{14}C-labelled tyrosine. *Above left*, two tumour cells showing silver grains, indicating presence of tyrosinase. *Right*, a cell (probably a macrophage) heavily laden with melanin but showing few silver grains and therefore tyrosinase-negative. Counterstained hæmatoxylin. (× 1200.)

No tumour cells were identified in blood, bone-marrow, or urine on the patient's first admission.

Further white-cell concentrates of venous blood were obtained, and in August, 1958, besides the melanin-containing phagocytes previously seen, small numbers of circulating tumour cells were found (*Fig.* 634). These were 21–24 μ in diameter, with round or slightly oval nuclei similar to those of endothelial cells, and with slightly cloudy pale-blue cytoplasm which in several examples showed a very fine peppering of melanin.

A DOPA reaction carried out on films of white-cell concentrates showed the normal positive reaction of granular leucocytes, while monocytes showed only slight or doubtful positivity.

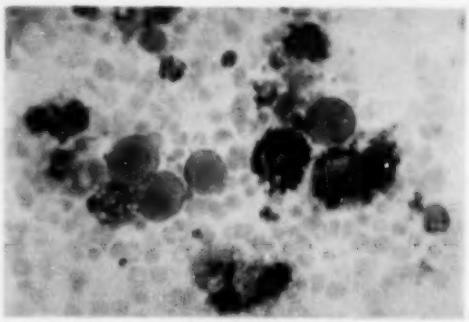

FIG. 635.—Deposit of peritoneal fluid. The cells containing large amounts of melanin are macrophages. The round cells with finer pigmentation are melanoma cells. May-Grünwald-Giemsa. (× 330.)

FIG. 637.—Showing the dusky-grey pigmentation, the distended abdomen, and the primary growth.

The peritoneal fluid examined on Nov. 16, 1958, was heavily blood-stained. Films of centrifuged deposit showed abundant red cells, lymphocytes, tumour cells and macrophages, and a few polymorphonuclear leucocytes (*Fig.* 635). The macrophages were tightly filled with melanin, mostly in the form of coarse irregular deposits. The cells interpreted as tumour cells bore a general resemblance to mesothelial cells, but had a higher nucleo-cytoplasmic ratio, and their cytoplasm showed a fine even peppering with the pigment; this varied in intensity, but the minute granules were mostly of uniform size and corresponded presumably to the melanin-forming organelles.

Autoradiographic Study.—The method was modified from Kukita and Fitzpatrick (1955). Air-dried smears of peritoneal fluid deposit were incubated for 16 hours with carbon-14 labelled tyrosine, and autoradiographs were then made to show the sites of tyrosinase activity. (The details of technique are given in the Appendix.) There was a marked concentration of silver grains over certain of the

large cells, especially those showing fine-to-medium melanin pigmentation, while the cells which were full of large lumps of melanin showed no increase of silver grains over the background level. This appears to confirm the identification of the former as tumour cells, and also

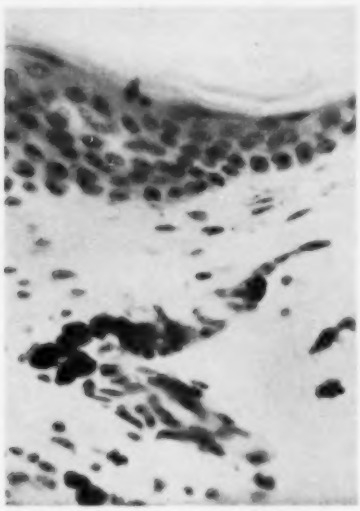

FIG. 638.—Section of skin remote from the tumour site. Macrophages containing melanin pigment are present in relation to the small blood-vessels of the dermis. Pigment granules are also present in the basal layer of the epidermis. (× 300.)

demonstrates the specific localization of the enzyme (*Fig.* 636).

AUTOPSY FINDINGS.—The following relevant abnormalities were found:—

Externally the body showed diffuse dusky-grey pigmentation especially of the upper half of the body. The sclerotics showed a brownish-yellow tinge. The abdomen was greatly distended. The primary growth previously described on the abdominal wall was 8 cm. in diameter (*Fig.* 637).

The *mucous membranes* of the oropharynx and respiratory passages was coloured pinkish grey. Apart from a few darkly pigmented areas in the left renal pelvis, the rest of the mucous surfaces were not pigmented.

The *peritoneal cavity* contained about 1500 ml. of dark-red fluid with chocolate-coloured clots. The ovaries (R. 1120 g., L. 1040 g.) were replaced by lobulated black masses of secondary tumour with central necrosis. No natural ovarian tissue could be demonstrated. The uterus and oviducts appeared natural.

The *liver*, *spleen*, and *kidneys*, and to a lesser extent the suprarenals and pancreas, showed a diffuse grey-black pigmentation. In the liver the normal markings were outlined by the black pigment.

The *bone-marrow* of the femur, iliac crest, vertebræ, ribs, and sternum all showed uniform grey-black pigmentation.

Small metastatic pigmented nodules were widespread in the dermis, in subcutaneous and subserous fatty tissue, in muscle, tendon, and connective tissue, and in the heart. A few were present in the brain, peribronchial tissue, intestinal wall, and liver. Lymph-nodes were replaced by tumour tissue in the cervical, axillary, and inguinal regions. No meningeal metastases were noted.

HISTOLOGY.—The primary tumour was a malignant melanoma consisting of columns and nests of pleomorphic cells containing fine melanin granules. Numerous pigment-laden macrophages were present in and around the tumour masses. The metastases showed the same structure.

Small *metastases* were widespread in fatty and connective tissue and striated muscle and in the heart, including

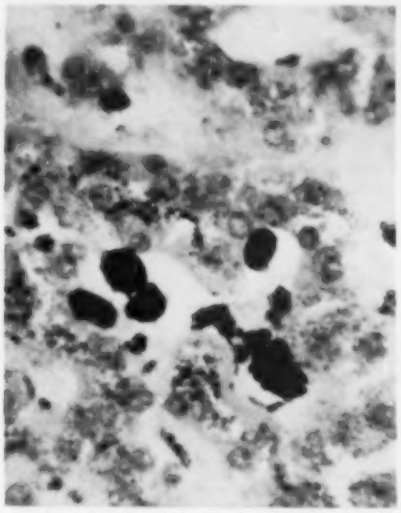

FIG. 639.—Section of liver. The Kupffer cells contain masses of pigment identifiable as melanin. The pigment visible in the parenchymal cells is not melanin. (*See* Appendix.) (× 325.)

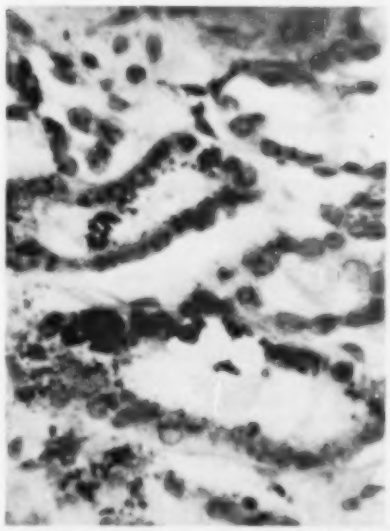

FIG. 640.—Section of kidney. Second convoluted tubules and collecting ducts contain melanin casts, and there is granular melanin in their lining cells. A small proportion of the pigment is not melanin. (*See* Appendix.) (× 325.)

the epi- and endocardium. A few metastatic nodules were also seen in the pancreas, thyroid, lung, liver, and gut.

In the skin adjacent to the primary tumour there were small foci of junctional activity, and localized granular

pigmentation of the basal layer spreading into the epidermis as far as the stratum corneum. In other areas of skin taken at random the epidermis was normal, but there were a small number of pigment macrophages throughout the dermis, especially in relation to the smaller blood-vessels (*Fig.* 638).

Melanin pigment macrophages were also frequently seen in the subserous connective tissue of the peritoneum

FIG. 641.—Section of thyroid, showing a small metastasis beside a large acinus. A fragment of melanin is present in the acinar colloid, and the lining cells are pigmented. (× 90.)

and in the suprarenals, spleen, bone-marrow, liver (Kupffer cells) (*Fig.* 639), and kidney. Much of the renal tubular epithelium contained granular melanin associated with melanin casts in the collecting tubules (*Fig.* 640).

In the thyroid discrete melanin granules were present near the terminal bar in the cells of a large acinus, adjacent to a small metastasis. The acinar colloid contained free melanin (*Figs.* 641, 642).

In the right orbital cortex, sections of a visible black spot showed an aggregate of pigment clumps which were not obviously intracellular. Some granular melanin could be seen within adjacent nerve-cells and astrocytes.

COMPARATIVE REVIEW OF HISTOLOGICAL MATERIAL FROM CASES OF MALIGNANT MELANOMA

In order to determine the frequency of melanosis in cases of malignant melanoma, we examined the material available in the files of the Department of Pathology, Radcliffe Infirmary, Oxford, over the past ten years.

Out of 32 cases of malignant melanoma with distant metastases which had been seen in the United Oxford Hospitals during this period, 7 had come to post-mortem examination. Of the surgical biopsy material, 2 cases provided specimens of liver and kidney tissue respectively. It was therefore possible to compare the incidence of tissue melanosis in the liver and kidney in 9 cases.

A search was made for any record of melanuria or of change of colour of the skin.

The findings are summarized in *Table I.*

The histological methods were the same as those used for liver and kidney in the present case, and are described in the Appendix.

The findings in this short series suggest that some general dissemination of melanin in the reticulo-endothelial system, together with melanuria, is a fairly common complication of malignant melanoma.

In *Case* 4 there was some diffuse pigmentation of the Kupffer cells in the absence of hepatic metastases, together with a moderate degree of renal tubular pigmentation. In *Cases* 3 and 9 there was melanuria, and the Kupffer cells were pigmented (this might be

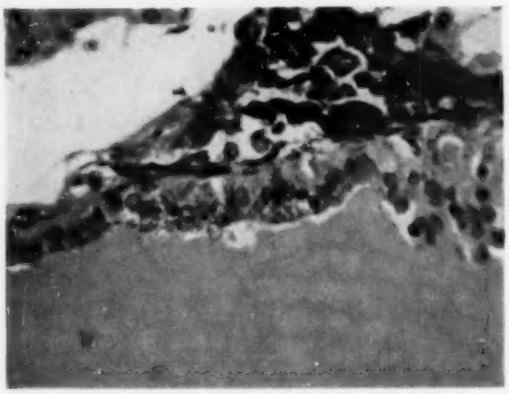

FIG. 642.—Section of thyroid (detail of *Fig.* 641). Discrete granular melanin is present near the terminal bar within the columnar cells of the acinus. A small metastasis is present beneath the basement membrane. (× 300.)

explained, however, by the proximity of hepatic metastases). *Case* 3 showed, in addition, renal tubular-cell pigmentation and a 'bronzed' skin.

In the remaining cases there was no tissue melanosis and melanuria was either absent or not recorded.

We therefore find 3 cases out of 9 in which evidence was found of generalized melanosis, but none of them presented the striking clinical picture seen in our own case.

DISCUSSION

1. Mechanism of Melanosis.—Melanin is normally synthesized by the melanocytes, which occur in the basal layer of the epidermis, the hair follicles, the choroid of the eye, and the leptomeninges. These cells are unique in containing tyrosinase, which catalyses the oxidation of tyrosine to dihydroxyphenylalanine (DOPA) and further to DOPA-quinone, from which melanin is readily formed (Fitzpatrick and Kukita, 1959). The conversion of DOPA to melanin can also be achieved by oxidases present in the granular leucocytes, and these are accordingly 'DOPA-positive' by Bloch's DOPA reaction; but they do not contain tyrosinase and do not form melanin *in vivo*.

Cells which carry melanin but which do not contain the tyrosinase which is necessary for the first stages of its formation are sometimes known as 'melanophores'. The property of taking up melanin

is widespread among phagocytic cells, and it is possible that they may be able to complete its formation from colourless intermediate substances.

Malignant tumours derived from melanocytes contain tyrosinase, often in very large amounts (Fitzpatrick and Kukita, 1959), and this is the explanation for their capacity to form large quantities of melanin. (Presumably the amelanotic growths have their tyrosinase inhibited.) In the rare cases of generalized melanosis such as the one which we have described, the pigment is mostly situated not in tumour cells, more examples will probably come to light. The melanoma cells themselves have already been discovered in the blood in several cases (Sandberg and Moore, 1957; Sandberg and others, 1958; Pruitt, Hilberg, and Kaiser, 1958; Roberts and Cole, 1959). In the present case melanoma cells contained either no melanin or a peppering of very fine granules, unlike the heavy granules present in macrophages (*Figs.* 633, 634); *and see* Alexander and Spriggs, 1960). The granules in the monocytes, however, were very fine.

Table I.—COMPARISON OF HISTOLOGICAL MATERIAL

SOURCE	DEPARTMENT OF PATHOLOGY NUMBER	MELANURIA	MELANIN IN KIDNEY TUBULES AND CELLS	MELANIN IN LIVER, KUPFFER CELLS	CLINICAL NOTES AND REMARKS
1. Post mortem	P.M. 596/51	—	None	None (Iron +)	Mitral stenosis. Single femoral metastasis
2. " "	P.M. 309/53	—	None*	None*	Metastases in brain, lungs, liver, and kidney
3. " "	P.M. 672/54	Positive	+ + with casts	+ + +*	Skin 'bronzed'. Dark urine. Liver showed numerous metastases
4. " "	P.M. 345/55	—	+	+	No liver metastases. Deposits in brain, stomach, pancreas, and lymph-nodes
5. " "	P.M. 212/56	—	None	None	Large metastases in brain (cheek melanoma)
6. " "	P.M. 520/56	Negative	None	None (Iron + +)	Yellow tinge to skin. Isolated liver metastases. Cerebrospinal melanosis
7. " "	P.M. 861/56	—	None	None	Brain metastases only ('amelanotic')
8. Nephrectomy	S.H. 6258/52	Negative	None*	—	Pedunculated single renal pelvic metastasis
9. Liver biopsy	S.H. 1960/55	Positive	—	+ + +*	Numerous metastases in liver

Blanks indicate absence of data.

* Metastases present in section.

tumour cells but in the cells of the reticulo-endothelial system and in the renal tubules (Katsurada, 1902; Weller, 1927); melanin precursors are also excreted in the urine.

According to Fitzpatrick and others (1954), the circulating substances are 'late' melanin precursors (such as the 5–6 hydroxyindole described by Dalgleish (1955) in melanuria). After being secreted by the 'melanin granules' of the melanoma cells, these substances are partly excreted in the urine and partly converted to melanin in the reticulo-endothelial cells by non-specific mechanisms.

Another explanation for the melanosis (but not for the melanuria) is the large-scale release of formed melanin pigment from necrotic tumour material. In the case which we have described there was extensive necrosis in two large ovarian metastases; moreover, the presence of melanin in circulating monocytes and macrophages is exactly what would be expected if a particulate 'ink' was being liberated into the circulation.

2. Cytological Diagnosis.—The finding of melanin in leucocytes of the blood seems only to have been recorded once in this century, by Liebmann (1929), the same case being studied post-mortem by von Albertini and Walthard (1927). More than fifty years earlier, before the introduction of staining methods in hæmatology, Nepveu (1872, 1874) and Liouville (1872, 1874) observed the same thing in finger-prick blood from 4 cases of melanomatosis. With the introduction of methods of concentrating the white cells in order to search for circulating

Melanin-containing cells have been found more frequently in the bone-marrow (Motulsky and Rohn, 1953; Franklin, Zavala, and Radcliffe, 1952), and in a few cases either melanoma cells or melanophores have been seen in serous effusions (Beneke, 1899; Judd, 1917; Ritz, 1949; Albeaux-Fernet and others, 1949; Spriggs, 1957). In the present case, the distinction between tumour cells and macrophages containing melanin could be clearly seen in the smears of peritoneal fluid. *Fig.* 635 shows tumour cells containing only a very fine peppering of melanin granules, while the phagocytic cells are heavily laden with large pigmented fragments.

The distinction between the two types of pigmented cell was also well shown in the autoradiographic study, in which the tumour cells (containing tyrosinase) are the only ones to be labelled (*Fig.* 636). One cannot, of course, be sure that the heavily laden cells are not tumour cells in which melanin formation had proceeded to its limit and in which tyrosinase activity has ceased, but this seems a less probable explanation.

3. Clinical Considerations.—The patient presented as a proved case of malignant melanoma with general skin pigmentation and numerous secondary deposits. It seemed justifiable to try the effect of steroids, and cortisone was therefore given in addition to a pethidine-chlorpromazine régime. It produced an immediate symptomatic improvement, which soon disappeared when, on two occasions, therapy was discontinued, but was restored each time the treatment was started again.

Cortisone inhibits the output of melanocyte-stimulating hormone by the pituitary, and this may be the explanation for the increased pigmentation seen in cases of adrenocortical insufficiency in which existing nævi become darker and new ones appear (Lerner, Shizume, and Bunding, 1954). There is also evidence from animal studies that ACTH controls the growth of melanocytes (Chavin, 1959). Destruction of the pituitary has unfortunately not been found of much value in the cases so far published (Shimkin, Boldrey, Kelly, Bierman, Ortega, and Naffziger, 1952; Pearson, Ray, Harrold, West, Li, Maclean, and Lipsett, 1956), but the numbers are still very small.

SUMMARY

A case of malignant melanoma is described, in which generalized skin pigmentation and melanuria developed. For the last 6 months of the patient's life melanin could be found in the monocytes of the circulating blood. Circulating tumour cells were also found 5 months before death. During most of this period she remained physically well, probably as a result of cortisone treatment. Before death she developed a peritoneal effusion containing malignant cells. These were demonstrated to contain tyrosinase by an autoradiographic method. At post-mortem examination there was generalized blackening of the major organs and of the whole reticulo-endothelial system. Histology showed aggregated melanin pigment throughout the cells of this system, including those in the dermis. Granular pigment was also present in the renal tubular epithelium and some thyroid acinar cells.

A review of recent post-mortem material is presented for comparison.

The possible mechanism of the syndrome is discussed.

APPENDIX

Method for concentrating White Cells from Whole Blood.—4 ml. of the patient's blood were added to 1 ml. of 6 per cent dextran solution containing 45 units of heparin per ml. The mixture was left until the red cells had sedimented. The supernatant fluid rich in white cells and platelets was then centrifuged and films were made of the deposit. They were stained with May-Grünwald and Giemsa as described in text-books of hæmatology; the histochemical methods for melanin are those recommended by Pearse (1953).

Autoradiographic Method for Tyrosinase.—Dried films of peritoneal fluid deposit were stored at −20° C. Before use, they were fixed in 70 per cent alcohol for 30 min. at 4° C. They were washed in water and incubated for 16 hr. in substrate at 37° C. The substrate consisted of 1 ml. of 0·1 M phosphate buffer *p*H 6·8 containing 0·01 mC. of l-tyrosine-^{14}C. It was Seitz-filtered before use.

After incubation the slides were washed in water for 2 min., then fixed again in 10 per cent formol saline for 1½ hr., washed in running tapwater for 3 hr., and dried.

Autoradiographs were then made by the Pelc stripping-film method as described by Lajtha (1954). Fourteen days' exposure was used, and in order not to darken the melanin the films were counterstained with hæmatoxylin only.

Methods for differentiating Melanin from other Pigments in Liver and Kidney.—

1. Perl's Prussian blue method for iron.
2. Sudan Black B (method of McManus) for lipofuscins.
3. Performic acid Schiff method (Pearse) for lipofuscins and phospholipids.
4. Autofluorescence in ultra-violet light. Formalin-fixed tissue in paraffin sections placed in xylol for 12–24 hr. to remove wax completely. Mounted under glass cover-slips with glycerin jelly or neutral mountant and examined by ultra-violet light using a dark-ground condenser.

Results showed that silver-positive pigment granules *in the liver parenchyma cells* were either autofluorescent (yellow-brown in our own case) or stained by one or other of the methods for lipofuscin or lipid pigments; *in the Kupffer cells* they were not stained by these methods (and gave a very small proportion of autofluorescent granules in our case only), and *in the renal tubular cells* they included a few autofluorescent granules and a small proportion of lipofuscin.

It was therefore concluded that the major proportion of the pigment seen in the latter two situations was melanin.

Acknowledgements.—We wish to thank Professor T. B. Fitzpatrick for much advice and help; Dr. L. G. Lajtha for the stripping-film autoradiograph; Mrs. G. M. Spriggs for drawing *Fig.* 634; Mrs. D. Jackson for photographing *Figs.* 636–642; and Professor T. Pomfret Kilner, Dr. A. H. T. Robb-Smith, and Mr. A. S. Till for their criticism of the manuscript. We also thank the British Empire Cancer Campaign, from which Dr. A. I. Spriggs is receiving a grant.

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DELAYED AFFERENT LOOP OBSTRUCTION FOLLOWING PARTIAL GASTRECTOMY

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ACUTE obstruction of the proximal loop of an antecolic gastrojejunal anastomosis following partial gastrectomy is a well-recognized early post-operative complication of that operation (Hensen, 1955). This lesion usually results in breakdown of the duodenal stump, but, on occasion, the development of persistent severe upper abdominal pain may lead to the early re-exploration of the abdomen, the distended afferent loop being thus discovered before free perforation of the duodenum has occurred (Smith, 1958; Watson, 1958).

Delayed obstruction of the afferent loop occurring months or even years after gastrectomy is less common, and is a complication bearing a high mortality. The majority of such cases are produced by herniation of the afferent loop through the space behind the gastrojejunal anastomosis, the various types of hernia involved having been well documented by Stammers (1954). Delayed obstruction of the afferent loop without herniation is quite rare and is not usually mentioned in discussions of the complications of partial gastrectomy. The present report details two examples of this uncommon condition encountered within six months.

CASE REPORTS

Case 1.—W. S., a retired male aged 71 years, was admitted to hospital complaining of upper abdominal pain which had been present for 20 hours. He had suffered from repeated attacks of asthma associated with chronic bronchitis and emphysema, and his respiratory disease had necessitated his admission to hospital on many occasions over the past eleven years. Nine years before the present admission he had had a Polya-type partial gastrectomy with an antecolic anastomosis performed for a chronic duodenal ulcer, and this operation resulted in complete relief of his dyspeptic symptoms. Three months prior to the onset of the present illness he had been admitted to hospital in cardiac failure associated with a flare-up of his respiratory troubles, and it was against this background of disability that he developed the attack of abdominal pain which led to his readmission. The intensity of his pain fluctuated in the initial period, but during the 6–10 hours immediately preceding admission it had become continuous and intense. He had vomited intermittently since the onset of this pain. Examination revealed a sick, thin, cyanosed man in obvious distress. He displayed the signs of chronic bronchitis and emphysema associated with those of mild residual cardiac failure. The abdomen was found to be distended and tight, and showed diffuse tenderness and release tenderness. No abnormality was found on rectal examination.

A diagnosis of acute intestinal obstruction was made and, after a period of cautious resuscitation, the abdomen was explored. When anæsthesia was induced an elongated broad mass could be felt in the upper abdomen, and on opening through the parietes this mass proved to be a greatly distended afferent loop leading up to the gastrojejunal stoma which had been formed following a high

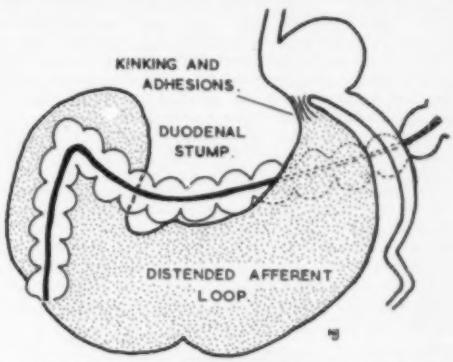

FIG. 643.—Diagram showing the findings on opening the abdomen in *Case* 1. The gross distension of the afferent loop and duodenal stump, and the kinking and adhesions giving rise to the obstruction, are indicated. The findings in *Case* 2 were identical to those shown above.

partial gastrectomy. This distended loop led back to a greatly distended duodenal stump. At the site of anastomosis the small bowel was acutely angulated and there were a few adhesions present. It was clear that the obstruction was occurring actually at the level of the gastric anastomosis, and that other than the presence of acute angulation there was no reason for this obstruction. The afferent loop was not herniated through the space behind the gastro-enterostomy (*Fig.* 643).

An aspirating needle was thrust into the distended duodenum and a large volume of clear bile-stained fluid aspirated. Following the deflation of the closed loop a Ryle's tube could easily be guided past the angulated area of the gastrojejunal anastomosis into the afferent loop and therefore the puncture wound in the duodenum was oversewn and the abdomen closed, the tube being left in position. During the operation there had been a marked decline in the general condition of the patient and in spite of continued efforts at resuscitation death occurred 12 hours post-operatively.

Autopsy confirmed that a high partial gastrectomy had been carried out and revealed a distended duodenum showing generalized inflammatory changes in its mucosal

coat, and these changes were found to have progressed to ulceration over an area 5 cm. in diameter close to the closed duodenal stump.

Case 2.—M. S., a seaman aged 51 years, was admitted to hospital with an 8-hour story of severe upper abdominal pain. He had had ulcer dyspepsia for many years and three years prior to admission had had an operation for closure of a perforated chronic duodenal ulcer. The dyspepsia continued unabated, and 12 months after his perforation a partial gastrectomy was performed resulting in complete relief of his symptoms. His present illness had commenced with pain of sudden onset situated in the upper abdomen. This pain had increased rapidly in severity and extent and at the time of admission was present throughout the abdomen. Vomiting had been associated with the pain, but had not been a marked feature of his illness.

He was a well-nourished man showing the signs of profound dehydration and shock, his blood-pressure being recorded as 70/50 mm. Hg, and his pulse-rate as 140 per minute. The abdomen was distended and rigid and general systemic examination was clear. A tentative diagnosis of perforated anastomotic ulcer was made and active resuscitation commenced. These measures resulted in only slight improvement in the general condition of the patient and therefore laparotomy was undertaken.

On opening the abdomen a large volume of clear fluid escaped and it was noted that there was gross retroperitoneal œdema. The most obvious feature, however, was a greatly distended afferent loop and duodenum, the obstruction being due to kinking and angulation at the site of the jejunal anastomosis. Once again it was noted that the initial gastrectomy had been extensive and that there was no cause for the obstruction other than the angulation and adhesions at the anastomotic site. The distended afferent loop was deflated, detached from the stomach, and implanted into the side of the efferent loop. During operation the general condition of the patient deteriorated further and he died 10 hours post-operatively.

Autopsy confirmed that a high partial gastrectomy had been performed, only 7 cm. of lesser curvature remaining. The duodenal stump and afferent loop were greatly distended and two acute tension ulcers were detected at the closed end of the stump. One of these had penetrated into the retroperitoneal tissue and had given rise to an extensive retroperitoneal cellulitis.

DISCUSSION

Reference to the available literature makes it clear that delayed obstruction to the afferent loop is a rare complication of partial gastrectomy. Goodall, Hindman, and Heimlick (1951) record a case occurring 5½ months after gastrectomy. There was some evidence of obstruction of the afferent loop in their case, but it is difficult to ascertain from their account whether the perforation resulted from a stitch abscess in the duodenal wall, which chanced to rupture both into the duodenum and into the general peritoneal cavity, or whether obstruction *per se* was the causative factor. Sanchez (1945) is stated to have encountered a similar case occurring 10½ months post-operatively. Reiner (1955) describes a case occurring in the fourth post-operative week, the patient having had mild obstructive symptoms in the early post-operative period. Rasch and Strange (1955) describe a patient in whom perforation of the duodenal stump occurred 4 months after partial gastrectomy, and Smith (1953) describes a case occurring in the ninth month.

This complication is to be clearly differentiated from delayed obstruction due to volvulus of, or herniation of, the afferent loop. In the cases referred to above, and in those described in the present paper, there was no evidence of rotation of the bowel or of herniation related to the gastrojejunostomy; in fact the obstruction if present seemed to be due merely to kinking and angulation at the site where the afferent loop joined the gastric remnant. Obstruction of the lower small bowel is not infrequently found to be due to angulation of the intestine produced by an adhesion, and it is clear that similar factors are involved in the production of delayed afferent-loop obstruction. The factors responsible for the onset of obstruction 9 years after the initial operation (*Case* 1) are as ill-defined as those responsible for a similar delay in the onset of the more common lower intestinal obstruction. Smith (1953) found, on exploring the abdomen, that the afferent loop had perforated and was therefore collapsed. He postulated that the obstruction was due to torsion of the loop and that following perforation the loop had untwisted. In view of the findings in the present cases this postulation seems to be unnecessary.

The afferent loop of a Polya gastrectomy is responsible for a significant number of both immediate and remote complications of gastrectomy and the cases described in the present publication, caused as they are by kinking and angulation, afford yet another reason for emphasizing that considerable care is required in the fashioning of the gastrojejunal continuity following gastric resection.

All too often the surgeon infolds an undue amount of gastric and jejunal wall on the lesser curvature side of the anastomosis, thus narrowing the lumen within the small bowel. Further, if this area of the anastomosis is fixed, high on the residual lesser curvature of the stomach, the angulation so produced may result in almost complete obliteration of the narrowed lumen at this critical point. It is preferable to reconstruct the lesser curvature of the stomach for some 5 cm. before commencing the gastrojejunostomy, thus reducing the risk of producing acute angulation at the site of anastomosis.

SUMMARY

1. Two cases of delayed afferent loop obstruction following partial gastrectomy are described.

2. It is suggested that angulation and kinking at the site of junction between the proximal loop and the gastric remnant is responsible for the development of obstruction, the condition being therefore comparable to the much more common small-bowel obstruction occurring as a late sequel of any abdominal operation.

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EXPERIMENTAL SURGERY

THE HEALING OF DEFECTS IN IMMOBILE SKIN IN RABBITS

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THE healing of full-thickness defects in the mobile skin of most experimental animals is due largely to the movement of the skin around the edges towards the centre of the defect, i.e., healing takes place by a process which may be called 'contraction'. In addition, a small and variable area of such a defect is covered by migratory epithelium. There are sites on the surface of the body, e.g., the inside of the ear, where the skin is immobile, and Billingham and Medawar (1955) suggested that repair in these situations is by a process similar to that seen in the healing of skin defects in man—namely, by contracture which results in deformation—and in addition "any residual gap not closed by contracture is occupied by a stable fibrous scar covered by skin epithelium of migratory origin". Despite this, in the course of a previous investigation one of the authors (Joseph, 1960) noticed that if an area of skin 15 × 15 mm. were removed from the inside of a rabbit's ear, the defect was covered by what appeared to be migratory epithelium in about 20 days without contracture.

Other investigators have studied the healing of defects of the skin of the ear but have usually used the outside where the skin is to some extent mobile (Henshaw and Meyer, 1944). Van den Brenk (1956), who used a modified Sandison-Clark ear chamber, stated that circular wounds larger than 15 mm. in diameter showed a growth of epithelium for 7 mm. and the central area of the wound remained uncovered by epithelium, and Spain and Loeb (1916) removed small areas, 2 or 4 sq. mm. By studying the healing of fairly large defects on the inside of the ear, it was hoped to determine whether contracture occurred and also to obtain information about the migratory epithelium and its underlying tissue.

MATERIAL AND METHOD

Adult rabbits of mixed stock weighing 2–3 kg. were used. Under nembutal anæsthesia, supplemented by ethyl chloride as required, the skin of the inside of the ear was cleaned with 1 per cent cetrimide and a square of 20 × 20 mm. was scratched on the skin. This area was centred on the main vessels running down the middle of the ear and its distal edge was about 4 cm. from the tip. The skin down to the cartilage was removed and, as suggested by Abercrombie, Flint, and James (1954), indian ink dots were placed on the skin about 1–2 mm. from each angle and the centre of each side (*Fig.* 644 A). The ear was dressed with penicillin tulle gras, surgical gauze, and plaster-of-Paris as described by Billingham and Medawar (1951). After 5 days for the 5-day specimens and after 10 days for all the others, the dressings were removed and no further dressings were applied. Both ears were used in all the rabbits. Photographs after the operation and at intervals of 5–10 days were taken. This general technique was followed throughout the investigation. As a result of the histological appearances after 5 and 10 days in some of the specimens, it was suspected that epidermal elements (hair follicles, sebaceous glands) were left behind and the denuded area was being covered by epithelium derived from these structures as well as from the epidermis at the edge of the wound. To confirm this, 8 specimens were taken out immediately after the skin had been removed. Sections at 200 μ intervals were examined and it was found that in 4 out of the 8 specimens some epidermal elements had been left behind. In order to solve the problem of removing the whole of the epidermis, together with all the hair follicles and glands, the cartilage was removed after removal of the skin. Unfortunately, this resulted in marked contracture of the whole ear following the loss of the splinting effect of the dressings, so that the final healed area was much smaller than 20 × 20 mm. The solution to the problem of making certain that all the epidermis had been removed while retaining the cartilage as a splint lay in the fact that in some of the specimens the exposed cartilage necrosed and separated over a period of 15–20 days, during which time the cartilage acted as a splint. Accordingly, 4 or 5 specimens of each period studied were obtained in which the cartilage had separated and the denuded area was covered by growth of epithelium only from the edges of the wound without apparent contracture of the rest of the ear. The absence of contracture was determined by the fact that the distance between the indian ink dots placed on the normal skin in the middle of the wound edges remained the same throughout the period of healing (*Figs.* 644, 645).

Specimens after 0, 5, 10, 15, 20, 30, 40, 60, 100, and 150 days were obtained. They consisted of the whole thickness of the ear and included the original denuded area together with 3–4 mm. of normal skin beyond it. These specimens were pinned on to cork and fixed in Bouin's fixative. Sections of all specimens were cut from the head end of the ear towards the tip at 7 μ, and 5 sections, each at an interval of 200 μ, were mounted on one slide so that each slide represented 1 mm. of the specimen. These were stained with hæmatoxylin and eosin. Many intervening serial sections were mounted and stained with van Gieson's and Lillie's modification of Masson's trichrome stain for collagen, Verhoeff's

stain for elastic fibres, Best's carmine stain for glycogen, periodic-acid Schiff technique for mucopolysaccharides and ground substance, and Gomori's modification of the Bielschowsky-Maresch method for reticulin fibres.

of the amount of growth of the epithelial edge after various intervals of time, the mean of the linear measurements of the new epithelium along the edges parallel to the sides of the ear at 1-mm. intervals some distance from the corners was determined.

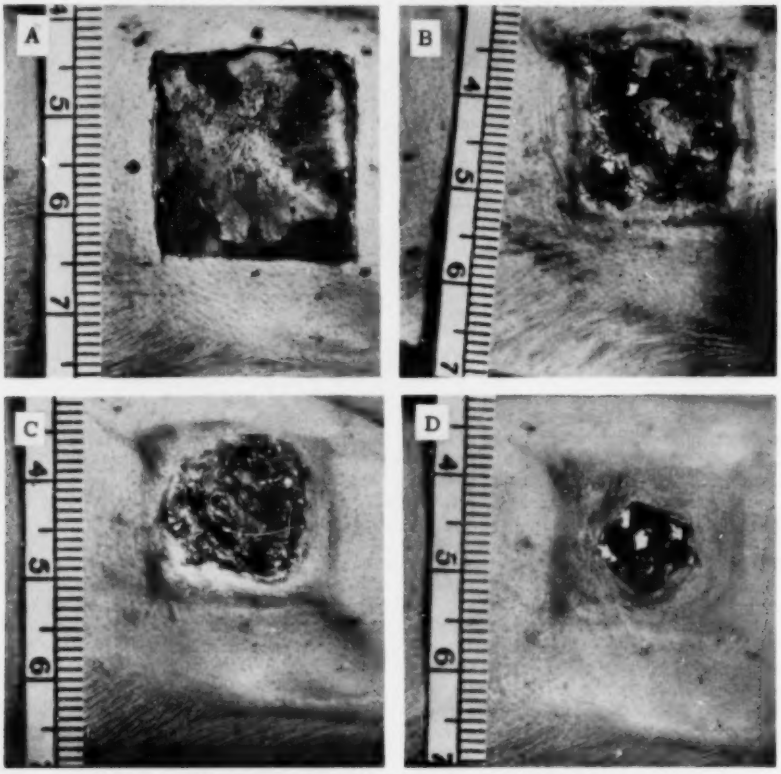

FIG. 644.—A, A denuded area, 20 × 20 mm., on the inside of the rabbit's ear with indian ink dots placed at each corner and at the middle of the sides. B, The appearance of the denuded area following removal of the dressings after 10 days. C, The appearance of the denuded area after 15 days. D, The appearance of the denuded area after 20 days.

Since it proved to be impossible to determine accurately the edge of the new epithelium either by direct vision or by photography owing to a scab which covered the growing edge, the horizontal growth of new epithelium was measured on the sections. At first this was done at intervals of 200 μ and the measurements, enlarged ten times, were plotted on to graph paper (*Fig.* 646). It was found that if the proximal and distal edges were plotted at intervals of 200 μ and the intervening sections at 1 mm., there was practically no difference in the final measurements of the growth of new epithelium. Subsequently all measurements were made in the latter way.

The area of the new epithelium and the remaining denuded area were measured by counting squares, and the area covered was expressed as a percentage of an original denuded area. This last measurement was obtained from the charts, since all the specimens showed some shrinkage which occurred chiefly during embedding. In order to obtain an estimate

OBSERVATIONS AND RESULTS

General.—When the dressings were removed the denuded area showed spread of epithelium from the edges and bleeding from the raw surface (*Fig.* 644 B). From 10–15 days little further epithelial spread took place (*Fig.* 644 C). This seemed to be due to the firm scab formed by the necrosing cartilage and clotted blood, which separated over the next 5–10 days. After 15 days removal of the edges of the separating scab showed epithelial growth underneath (*Fig.* 644 D). All denuded areas left for 40 days were completely covered by epithelium. As stated above, measurement between the indian ink dots showed that there was no contracture of the edges of the skin as is seen in the chest or flank of animals with a mobile skin. It could therefore be concluded that the covering of the denuded area was entirely by epithelial migration.

The epithelium covering the wound, although observed for up to 150 days, never took on the

appearance of the normal skin of the inside of the ear. At 40 days the denuded area was clearly delineated from the surrounding skin and the new epithelium was frequently irregular on its surface and redder than normal, with areas of silvery scales situated nearer the centre. During the next 30 days the scales became much less marked and the red surrounding parts became paler. The condition of the surface now became stationary.

In 13 out of the 16 specimens which were observed for 40 days or more, pigmented and non-pigmented hairs were seen usually nearer the lower edge of the new skin about 35 days after the original operation.

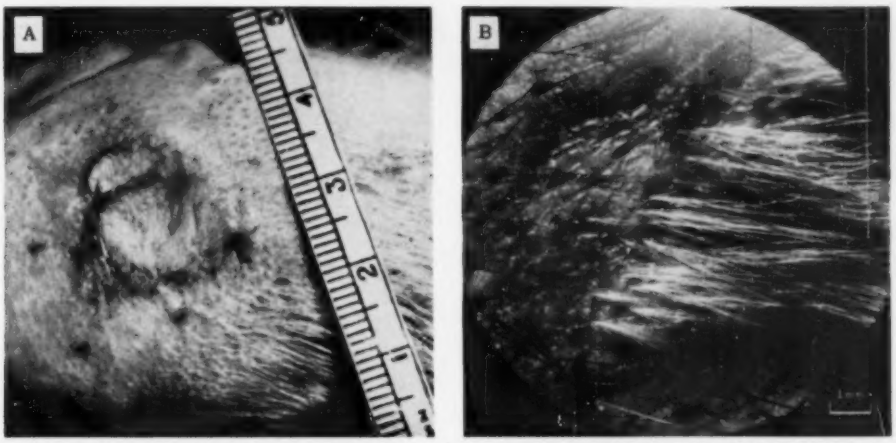

FIG. 645.—A, The appearance of a healed area after 60 days, showing a profuse growth of hairs directed towards the upper border of the ear. B, A photomacrograph (× 10) of a corner of a healed area, showing bundles of hairs. Compare these bundles with the single and double hairs emerging from depressions in the surrounding skin to the left and below.

Table I.—AREAS COVERED AND STILL DENUDED, AND ORIGINAL DENUDED AREAS MEASURED FROM THE CHARTS AFTER 5, 10, 15, 20, AND 30 DAYS

Period of Healing	*Area Covered*	*Area not Covered*	*Original Denuded Area*
days	sq. cm.	sq. cm.	sq. cm.
5	0·82	2·47	3·29
	0·79	2·26	3·05
	0·83	2·03	2·86
	0·84	2·12	2·96
	0·78	1·77	2·55
10	1·59	1·58	3·17
	1·53	1·58	3·11
	1·78	1·35	3·13
	1·70	1·38	3·08
	1·48	1·41	2·89
15	1·67	1·76	3·43
	1·83	1·58	3·41
	1·59	1·75	3·34
	1·81	1·55	3·36
20	2·22	0·72	2·94
	2·69	0·27	2·96
	2·49	0·38	2·87
	2·51	0·24	2·75
30	3·04	0·01	3·05
	2·94	0·01	2·95
	2·95	0·22	3·17
	2·87	0·04	2·91

Many of these hairs were pigmented as soon as they were observed. The striking features of these hairs were their large number (*Fig.* 645) and varied orientation, as compared with the number and regular orientation of the normal hairs on the inside of the ear.

Quantitative Studies.—*Table I* shows the total areas and the areas covered and still denuded of each specimen after 5, 10, 15, 20, and 30 days, and *Fig.* 647 shows each area covered by the spread of epithelium expressed as a percentage of an original denuded area. This area was always less than 4 sq. cm. owing to shrinkage which occurred in the course of the preparation of the sections. The mean of these areas for any single group is not significantly different from the mean of all the original areas (3·06 sq. cm.). It will be noted that after 5 days about 28 per cent of the denuded area was covered. There was practically no difference in the area covered (about 50 per cent) after 10 and 15 days, although spread of the epithelium downwards and sometimes underneath the separating cartilage was seen. This cessation of surface spread was due to the thick adherent scab to which reference has already been made. After 20 days about 87 per cent of the denuded area was covered, although by this time there was greater variation between the different specimens. After 30 days almost all the denuded area was covered. In all the 16 specimens removed after 30 days, the denuded area was covered.

Table II.—MEANS AND STANDARD DEVIATIONS OF THE GROWTH OF THE EPITHELIUM OF THE TWO EDGES PARALLEL TO THE SIDES OF THE EARS AFTER 5, 10, 15, AND 20 DAYS

Period of Healing	*Means and Standard Deviations of the Growth of Two Epithelial Edges*	
	A	B
days	mm.	mm.
5	1·20 ± 0·37	1·50 ± 0·38
10	3·04 ± 0·49	2·78 ± 1·12
15	3·70 ± 0·70	2·88 ± 0·45
20	5·60 ± 1·49	5·66 ± 0·82

Table II gives the means and standard deviations of the growth of two of the epithelial edges. There is no significant difference between the means of the two edges in each group, and it is estimated that the edge of the migratory epithelium advanced about

1·4 mm. after 5 days, 2·9 mm. after 10 days, 3·3 mm. after 15 days, and 5·6 mm. after 20 days. The smallness of the advance of the epithelium between 10 and 15 days was to some extent more apparent than real, since during this time the epithelium

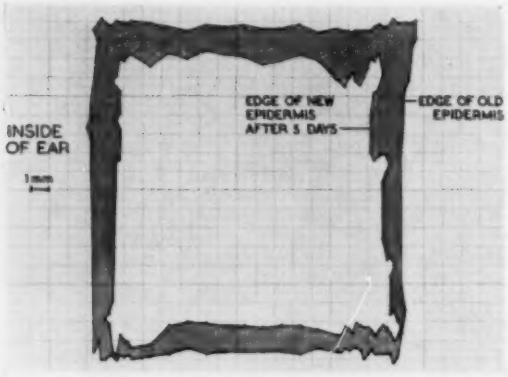

FIG. 646.—A 5-day chart showing the method used for obtaining the outline of the edge of the migrating epithelium and measuring the original denuded area.

could be seen to be growing downwards outside the separating scab. This growth, however, did not contribute directly to the covering of the denuded area. After 20 days or somewhat earlier, the denuded area became rounded in shape instead of square, owing to the area at the corners receiving epithelium from both edges. It was difficult to estimate how far the epithelium had advanced after 30 days since the denuded area was small, frequently broken up, and not in the centre.

and epidermis as papillæ, one can only state that they are flat, and well-marked papillæ are not seen. Hair follicles are seen at intervals of about 1 mm. and one or two hairs emerge from holes in the epidermis, except near the lower edge and tip where

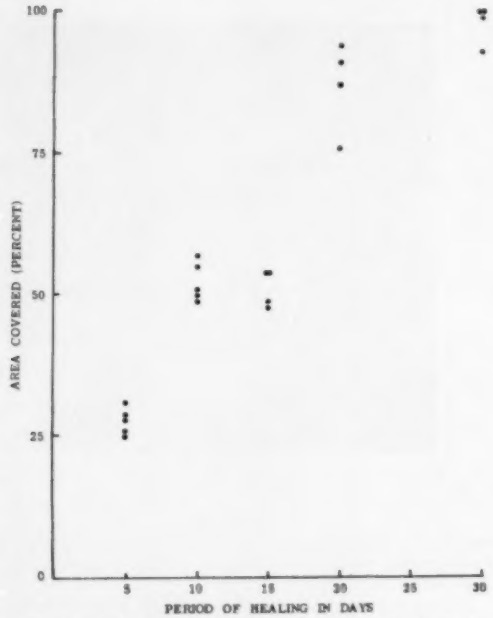

FIG. 647.—A graph showing the percentage of the original denuded areas covered after different intervals.

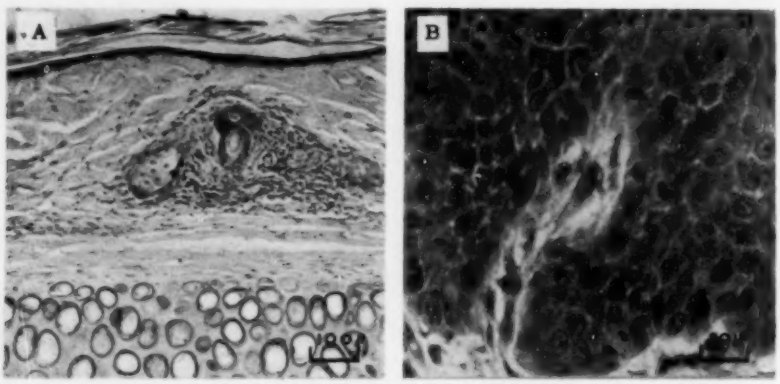

FIG. 648.—A, A section showing the histology of the normal skin of the inside of the rabbit's ear. B, A 5-day section showing mitotic figures in the thickened epithelium just behind the migrating epithelium.

Histology.—The epidermis of the skin of the inside of the ear in the rabbit has four to six layers of cells, with a distinct basal layer of columnar cells. The stratum spinosum contains only small amounts of glycogen. 'Clear' cells are fairly common and mitotic figures are few. The stratum corneum is thin and the quantity of keratin small. If one can describe the undulations of the junction between the dermis clusters of many hairs are seen. These hairs point towards the tip except along the lower border, where they are directed towards the edge. There are usually two or three sebaceous glands associated with a hair follicle (*Fig.* 648 A).

The normal dermis consists of large, collagenous fibres running transversely, but nearer the surface they are more loosely arranged and tend to run in

the opposite direction. There are few reticular fibres and these are more numerous around the hair follicles. There are fewer elastic fibres than in mobile skin and they lie near the epidermis and often perpendicular to it. The dermis is relatively acellular and only small blood-vessels are seen. It is difficult to differentiate the dermis into two layers and to distinguish clearly between the deeper layers of the dermis and the outer surface of the perichondrium.

After 5 days the new epithelium could be divided into two parts—an older which was near the edge of the denuded area and many layers thick (10–15), and a newer which was only 1 cell thick. In the former many mitotic figures in or near the basal layer could be seen (*Fig.* 648 B) and the epithelium could be easily divided into the classical layers—stratum germinativum, etc. The cells were larger than normal. There was an increase of glycogen, slight in the stratum germinativum and marked in the stratum spinosum. More mitotic figures than normal were seen in the epidermis adjacent to the original edge of the wound. A mitotic figure was occasionally seen in the thin spreading epithelium consisting of a single layer of cells (*Fig.* 649 A). The cells of the edge had processes which became easily visible if they had been slightly pulled away from the underlying granulation tissue (*Fig.* 649 B). The latter showed no special features and consisted of the usual mixture of mesenchymal cells, leucocytes, and red blood-cells. Mucopolysaccharides were present in considerable quantities in the granulation tissue.

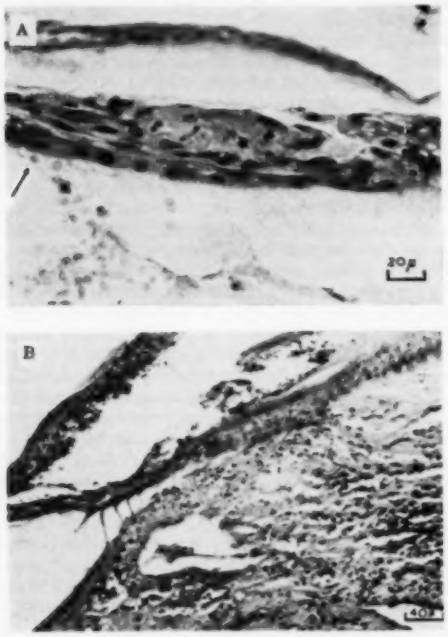

FIG. 649.—A, A 5-day section showing a mitotic figure (arrow) in the migrating epithelium. B, A 5-day section showing the processes of the migrating epithelial cells made visible owing to their partial separation from the underlying tissue.

After 10 days, apart from further spread over the denuded area, the epithelium did not show many changes. Keratin, however, could be seen over the oldest part of the new epithelium and was much thicker than normal, and its deep surface was very irregular. As compared with that of 5 days, the granulation tissue lying below the new thick epidermis was much more cellular and organized, with fewer blood-cells. There were no elastic fibres and few collagen fibres, but a large quantity of reticular fibres was found running in all directions.

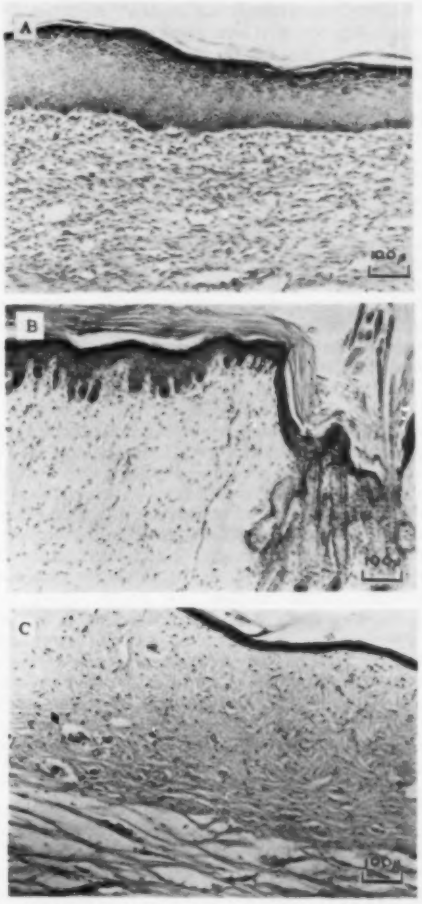

FIG. 650.—A, A 15-day section showing a particularly large number of mitotic figures in the epithelium behind the migrating epithelium. B, A 100-day section showing (*a*) well-marked rete pegs, (*b*) a bundle of hairs. Compare with *Fig.* 648. C, A 100-day section showing the new 'dermis'. Compare with *Fig.* 648 for cellularity, density of fibres, and arrangement of layers.

After 15 days, the situation was complicated by the peculiar experimental conditions of this investigation. The epithelium continued to spread, but by this time the cartilage of the ear was beginning to

separate and the epithelial growth was downwards rather than horizontal. The epithelium did not present any special new features, but its proliferation was very marked and irregular and might even extend in a direction opposite to that of the denuded area. Mitotic figures were frequently seen in the thickened epithelium near the spreading edge and were more numerous than in the 'older' new epithelium (*Fig.* 650 A). There was still a marked increase of glycogen granules in the new epithelium. The organizing granulation tissue did not show any marked changes as compared with that seen at 10 days.

After 20 days the following changes were seen. Cells containing pigment appeared in some of the specimens of the stratum germinativum near the edge of the original denuded area and the rete pegs of the epithelium were more marked. The granulation tissue contained more collagen fibres, less reticulin, and fewer cells, and its deeper layers resembled those of the normal skin. In the more superficial parts, however, the fibres ran in all directions. Elastic fibres appeared but they were fewer and finer than normal and were seen in the older part of the new 'skin'.

The appearances described indicate the main changes which occurred in the denuded area and even at 20 days the changes were much more advanced in the more peripheral parts than in the central. From 30 days onwards the definitive new epidermis had about 10 layers of cells which were larger than those of the normal skin, and the stratum granulosum was especially thickened. Subsequently, much of the epidermis became thinner. The keratin flakes were more numerous and longer and the rete pegs were more numerous and marked (*Fig.* 650 B). The glycogen at 30 days was still in excess of normal but patchy in its distribution. By 100 days the glycogen became normal. In the granulation tissue the reticulin fibres decreased and the collagen and elastic fibres increased in quantity. These changes were more or less complete by 60 days, by which time the mucopolysaccharides were normal. By 60 days the pattern of the fibres had also become fairly uniform. The elastic fibres were normal in size and quantity and the collagen fibres formed two distinct layers, a deeper running transversely and a more superficial running longitudinally and obliquely (*Fig.* 650 C). The cells of this connective tissue were rounder, paler, and more numerous than those of the normal dermis. Hair follicles and sebaceous glands were not seen in the new epidermis until 40 days and only in some of the specimens. The striking feature of these hairs was their large number as compared with that normally seen in this region of the ear (*Fig.* 650 B).

No changes were detected in the present studies between 100 and 150 days.

DISCUSSION

All quantitative investigations into the rate of the covering of a denuded area are influenced by the methods used by the investigators. The rate of covering of a denuded surface is dependent on the experimental animal (Spain, 1915), the site of the denuded area (the extent of the mobility of the skin), the size of the wound (Spain and Loeb, 1916), the type of dressing (Lindquist, 1946), the shape of the wound (Henshaw and Meyer, 1944), the frequency of the application of the dressings (Billingham and Russell, 1956a, b), and the method of measuring the advancing epithelial edge, to name only a few of the possible variations in technique. One can only say, therefore, that, given the experimental conditions of the present investigation, a denuded area 20 × 20 mm. will be covered in about 30 days by epithelium spreading inwards from the edge. It is important to stress the fact that the healing was delayed while the scab, consisting mainly of the necrosed cartilage, was separating. The delay caused by a scab was commented on by Loeb (1920).

There have been no previous studies of the rate of epithelialization of a denuded area of this size and shape on the inside of a rabbit's ear, but Henshaw and Meyer (1944) made a similar investigation on the outside of a rabbit's ear where the skin is slightly mobile. Their wounds were not dressed at any time and measurements were made with callipers and from photographs. They found that areas of approximately 20 × 20 mm. were epithelialized in about 15 days. Their more rapid epithelialization may be due to the absence of an adherent scab in the experiments reported here and/or some movement of the edge of the skin on the back of the ear by contraction.

Lindquist (1946), using rats, prevented the contraction of the wound edges of a denuded area on the flank and found that wounds of about 300 sq. mm. were covered in about 20 days. Breedis (1954), using rabbits, prevented the contraction of the edges of circular denuded areas on the flank 25 mm. in diameter (about 400 sq. mm.) and found that the wound was covered with epithelium "several additional days" after 30. These figures correspond more or less with those reported here. Van den Brenk (1956), using ear chambers and circular denuded areas on the back of the rabbit's ear, found that areas of about 80 sq. mm. were covered in about 25 days and that areas of more than about 170 sq. mm. (circular areas with a diameter of more than 15 mm.) showed a cessation of growth after the epithelial edge advanced about 7 mm. The comparatively slow rate of epithelialization and final non-epithelialization of the centre of his larger wounds might have been due to his experimental conditions.

Regarding the rate at which the epithelial edge advances, Howes (1943) estimated that after a latent period of 3–6 days the average rate was 0·5 mm. per day, with some variation from day to day. Van den Brenk (1956) estimated that the advance was 0·2 mm. per day. The results reported here, about 1·4 mm. after 5 days, about 1·5 mm. between 5 and 10 days, and about 2 mm. between 15 and 20 days, are more in agreement with the former figure.

The important features of the histological findings were the increase in, and distribution of, the mitotic figures, the appearance of pigment in the new epithelium after 20 days, the appearance, number, and direction of the hairs in the new epithelium, and the formation of marked rete pegs which persist after 150 days. The initial increase and subsequent decrease in the number of layers in the new epithelium, the increase and decrease in the glycogen, the changes in the granulation tissue, and the changes in the mucopolysaccharides corresponded with the observations made by other workers. It is

interesting to speculate whether or not the necrosing cartilage increased the amount of mucopolysaccharides in the wound area and thus stimulated the healing process and particularly the migration of the epithelium (Penney and Balfour, 1949; Layton, Frankel, Sher, Scapa, and Freidler, 1958).

With regard to mitoses, there is general agreement that they increase in number in the normal epithelium next to the wound edge in the early stages of healing. There is some controversy regarding whether they are seen in the epithelium over the denuded area before it is covered by the spreading epithelium (Hartwell, 1955). There can be no doubt that in the present investigation they were seen in large numbers in the new epithelium, which was thickening behind the advancing edge, long before the whole denuded area was epithelialized. This has also been observed by Spain and Loeb (1916) and Howes (1943). It appears likely that the reported differences depended on the size of the denuded area and the speed with which the denuded area is covered, as suggested by Arey (1936). Bullough and Lawrence (1957), using the ears of mice, did not see any mitoses in the spreading epithelium until the wound area was covered. Their wounds, however, were small and were covered in 48 hours. Even more controversial is whether or not mitoses occur in the spreading epithelium. These have been seen in the present experiments, but their presence does not contradict the view that moving cells do not divide (Burrows, 1927). It is conceivable that movement of the cells in the advancing epithelium was intermittent and that during a resting phase mitosis could occur. It is difficult in any case to determine the exact change from the advancing edge to the thickening epithelium just behind this edge. If, however, the direction of the long axis of the nucleus (parallel to the surface) is a criterion of the advancing edge, then mitoses were fairly often seen among these cells.

The appearance of pigment in the basal layer of cells and the fact that it appeared after only 20 days were unusual features. This was probably due to the fact that melanocytes from the old skin adjacent to the edge of the wound migrated into the new epithelium either with the spreading epithelium or subsequently. Howes (1943) noticed pigmentation after 1 week in the epithelium, which spread over the denuded area on the back of the rabbit's ear.

It has usually been stated that hairs do not grow on the epithelium which covers a scar (Brown and McDowell, 1942). Breedis (1954) found that hairs and sebaceous glands developed in the scars of wounds which had been prevented from closing by contraction, and Billingham and Russell (1956a, b) described the growth of new hairs from the central scar in incompletely contracted wounds on the flanks of rabbits. The latter called this phenomenon 'hair neogenesis'. It may be added that Straile (1959) repeated Breedis's experiments and found that he could not prevent contraction of the wound with the same technique. He concluded that the new hairs were really hair follicles from the edge of the wound which repopulated the entire wound area except for a small central scar which remained hairless. The striking features of the hairs which grew from the new epithelium in the experiments reported here were their numbers and orientation as compared with the hairs on the rest of the inside of the ear. As many as 15 follicles were seen in one group, and this is seen normally only in the edge of the inside of the ear. In general the hairs sloped towards the centre of the wound, but this varied to some extent. In view of their numbers and their concentration near the lower edge of the wound where the adjacent hair follicles form much larger clusters than elsewhere, it is suggested that these hair follicles developed from hair-follicle cells which contributed to the migrating epithelium.

Finally it may be stated that the well-marked rete pegs of some areas of the new epithelium constituted an unusual feature which has not been reported before. It is this, together with the other features of the new epithelium and underlying scar tissue, which prompts the suggestion that although the tissue over the denuded area is not the same as the skin which was removed, new 'skin' functionally as efficient as the surrounding skin was formed. This new 'skin', although its structure is not homogeneous, is not the easily injured, pale, thin, hairless, scar tissue usually described, but is as tough and thick as the rest of the skin of the inside of the ear.

SUMMARY

1. An area of skin 20 × 20 mm. was removed from the inside of the ears of rabbits for the purpose of studying the way in which defects in immobile skin healed.

2. In order to be certain that all the skin together with the hair follicles and sebaceous glands was removed and that the splinting action of the cartilage was retained until healing was almost complete, only specimens in which the exposed cartilage necrosed were used. In these conditions, it was found that contracture did not occur.

3. The migration and growth of the epithelium from the edges were determined by measurement of sections at known intervals. By this method it was found that of the denuded area about 28 per cent was covered after 5 days, 50 per cent after 10–15 days, and 87 per cent after 20 days. Coverage was complete by about 30 days.

4. The advance of the edges parallel to the sides of the ear was estimated to be about 1·4 mm. after 5 days, 2·9 mm. after 10 days, 3·3 mm. after 15 days, and 5·6 mm. after 20 days.

5. The 'skin' which covered the denuded area showed interesting features with regard to mitotic figures during the spread of the epithelium, pigment in the deeper layers of the epidermis, rete pegs, and growth of hair.

6. It is suggested that the tissue which covers the denuded area, although unlike the surrounding skin, is in many respects functionally as efficient as the normal skin of this region and should be called skin.

Acknowledgements.—We wish to thank the Endowments Committee of Guy's Hospital and the Clinical Research Committee of Guy's Hospital Medical School for generous grants towards the expenses of this investigation; Mr. A. N. Finch for the photomicrographs; and the Department of Medical Illustration, Guy's Hospital, for the preparation of the photographs and charts.

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THE HEALING OF EXPERIMENTAL GASTRIC ULCERS

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WE have still to discover why peptic ulcers in humans fail to heal and become chronic. This root of the peptic ulcer problem was emphasized by Cohnheim (1882) nearly 80 years ago and it is as cogent to-day as it was then. There are numerous methods of producing acute peptic ulcers in laboratory animals and it is well known that in the stomach such ulcers heal rapidly. Spontaneous chronic gastric ulcer is, however, unknown in laboratory animals and, because of this fact, it follows that *any* method which induces chronicity in experimental gastric ulcers will be biologically significant. The investigations outlined here are concerned with attempts to produce such impairment of healing.

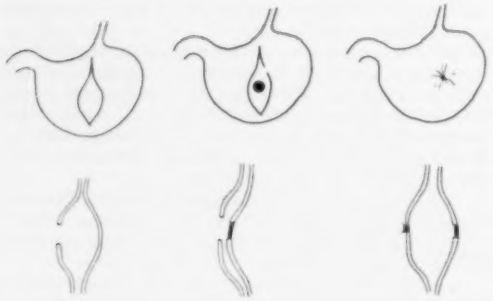

FIG. 651.—Production of cautery ulcer in stomach: stages in the operation. Ventral (A) and sectional (B) views of (1) Gastrostomy; (2) Ulcer produced; (3) Gastrostomy sutured.

METHODS

An acute gastric ulcer was produced in adult female guinea-pigs by a simple technique (Williams, 1953). Stainless steel brands, 2, 4, or 12 mm. in diameter, were heated in a small flame of constant size for about 20 sec. and then applied to the mucosal surface of the posterior wall of the stomach at its centre, after laparotomy and gastrostomy under ether anæsthesia (*Fig.* 651). They were applied with slight pressure until the sensation of heat felt by an underlying finger-pad on the serosal surface became uncomfortable. Afterwards the gastrostomy orifice was closed with a purse-string suture and the abdominal wall stitched in two layers.

The ulcers were well-defined, circular lesions (*Fig.* 652) extending to the serosa, and healed rapidly.

FIG. 652.—Ulcer, initially 4 mm. diameter, in guinea-pig stomach 4 days after production. (× 4·5.)

All ulcers initially 4 mm. in diameter (the most common in these experiments) healed by the seventeenth post-operative day. Most ulcers 12-mm. in diameter healed by the twenty-first day and all by the thirtieth day after operation. When animals were killed at the end of an experiment, the stomach was filled with 10 per cent formalin and then immersed in this fixative for 24 hours; it was then opened and the mucosa washed very gently under

a small stream of water. The healing or healed lesion was usually easily identified on a background free of folds. Identification was further facilitated by prior 'tattooing' of the ulcer site with indian ink at the time of the operation. Using a minimum of 10 guinea-pigs in each experiment, many attempts were made to delay the healing of such acute ulcers to induce chronicity. The investigations are summarized as follows:—

Mechanical Irritation.—Linen or silk thread was incorporated into the stomach wall prior to cauterizing the site with a 4-mm.-diameter brand. The animals were killed 17 days later.

Hydrochloric Acid.—The ulcer was subjected to an excessive acid environment by chemical and mechanical means:—

1. Ten guinea-pigs were given intramuscular injections of histamine dihydrochloride in beeswax (1·5 mg. histamine base per kg.) twice a day after a 4-mm. ulcer had been produced in the middle of the posterior wall of the stomach. This preparation is known to stimulate the production of a large volume of highly acid gastric juice for 24 hours or more (Code and Varco, 1940). The animals were killed 17 days later.

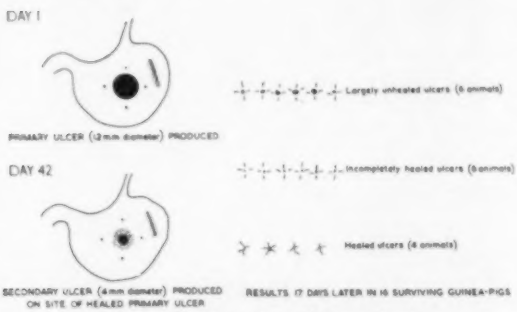
DAY 1
Largely unhealed ulcers (6 animals)
PRIMARY ULCER (2 mm diameter) PRODUCED
DAY 42
Incompletely healed ulcers (6 animals)
Healed ulcers (4 animals)
SECONDARY ULCER (4 mm diameter) PRODUCED ON SITE OF HEALED PRIMARY ULCER
RESULTS 17 DAYS LATER IN 16 SURVIVING GUINEA-PIGS

FIG. 655.—Healing of 'secondary' gastric ulcers.

2. Laparotomy was performed in 10 guinea-pigs and a 'wasp-waist' narrowing of the mid-portion of stomach produced by tying a linen ligature, partially threaded through the wall (*Fig.* 653). An incision was then made in the anterior wall of the proximal compartment and a 4-mm. ulcer produced on the posterior wall, just proximal to the stenosed segment. The gastrostomy and abdominal wall incisions were then sutured and the animals were killed 17 days later.

3. A further attempt to delay healing by causing retention of gastric juice was performed as follows: a 4-mm. ulcer was produced within a small pouch which had been made by partially isolating a segment of stomach about the middle of the greater curve, using a linen ligature threaded through the stomach wall (*Fig.* 654).

Alcohol.—Concentrated solutions of ethyl alcohol produce considerable mucosal damage when introduced into the stomach (unpublished personal observations). An experiment was therefore undertaken to determine whether the healing of experimental gastric ulcers could be impaired by the daily administration of alcohol into the stomach.

An ulcer 4 mm. in diameter was produced in the standard way described in 30 guinea-pigs. The animals afterwards received 4 ml. 60 per cent alcohol by stomach tube each day for 17 days.

Secondary Ulcers.—The healing of a small cautery ulcer produced on the scarred site of a larger ulcer was investigated in 24 guinea-pigs. An acute ulcer 12 mm. in diameter was produced on the

FIG. 653.

FIG. 654.

FIG. 653.—Production of cautery ulcer in guinea-pig stomach just proximal to a stenosed segment.

FIG. 654.—Production of cautery ulcer in a pouch of guinea-pig stomach.

posterior wall of the middle of the stomach. Six weeks later, a smaller (4 mm. diameter) ulcer was produced on the scarred site of the first ulcer (*Fig.* 655). The animals were killed 17 days after this second operation.

'Ring Burns'.—The effect of ischæmia on the healing of gastric ulcers was investigated in 2 experiments in which a burn, 12 mm. in diameter and 2 mm. in breadth, was made with a steel ring around a 4-mm. ulcer (*Fig.* 656). The ring was applied momentarily to the mucosal surface in one experiment and

FIG. 656.—Ring burn around medium-sized ulcer on posterior wall of stomach.

to the serosal surface in another experiment. The animals were killed 17 days later.

Local Injections.—Various substances were injected into the stomach wall at the proposed ulcer site prior to cauterization in an effort to delay healing. In previous (unpublished) investigations the author had observed that Freund's adjuvant provoked an inflammatory reaction and the formation of granulation tissue when injected into the stomach wall, so this substance and its components were tested for their possible delaying effect on healing. Live tubercle bacilli (B.C.G.) were also injected. Another substance injected was carrageenin, a sulphonated polygalactose derived from Irish moss, which when injected subcutaneously into guinea-pigs produces a granuloma rich in collagen (Williams, 1957). Ferrous sulphate was another agent injected because the author (unpublished work) had previously observed that this salt damaged gastric epithelium when introduced into the stomach cavity of both guinea-pigs and man.

1. Using a tuberculin syringe and a fine needle, 0·5 ml. of the following substances were injected into the stomach wall in separate experiments and

afterwards a 12-mm. ulcer was produced at the injection site:—

a. Freund's adjuvant, viz.:—

Light paraffin oil (Bayol F), containing 1 mg. /ml. dried, killed tubercle bacilli	2 parts
Emulsifying agent derived from Lanolin (Falba)	1 part

b. Light paraffin oil (Bayol F) alone.

c. Mineral oil (Bayol F) and emulsifying agent (Falba) in equal parts, without added tubercle bacilli.

d. One per cent carrageenin.

The animals were killed 30 days later.

2. (*a*) 0·2 ml. B.C.G. vaccine was injected into the stomach wall, the site being marked with indian ink. Six weeks later, the stomach was re-opened and a 4-mm. ulcer produced at the injected site. The animals were killed 17 days later. (*b*) 0·2 ml. B.C.G. vaccine was injected intramuscularly into the hind limb of a guinea-pig. Six weeks later 0·2 ml. 1–1000 old tuberculin was injected intradermally and a positive sensitivity reaction was noted. Laparotomy and gastrostomy were then performed and 0·5 ml. 1–1000 old tuberculin injected into the stomach wall, then a 4-mm. cautery ulcer produced at the site of injection. The animals were killed 17 days later.

3. 0·5 ml. 1 per cent ferrous sulphate was injected into the stomach wall and a 4-mm. ulcer produced at the injected site. The animals were killed 17 days later.

RESULTS

Normal Healing.—This has been described in detail (Williams, 1953). Normal repair is a neat, orderly process in which there are two main components—namely, epithelial regeneration and fibrosis. A thin film of epithelium grows over the ulcer floor from the necks of the marginal glands (*Fig.* 657) and becomes firmly adherent to the floor. After an initial intense leucocytic activity, with removal of necrotic debris, the floor becomes transformed first into granulation tissue and then into mature fibrous tissue, and simple glands develop from the epithelial film (*Fig.* 658). It was originally thought that there was no specialized differentiation of the cells constituting the deeper portions of the glands, but the author has observed well-formed oxyntic and chief cells in healed ulcers 3 months old.

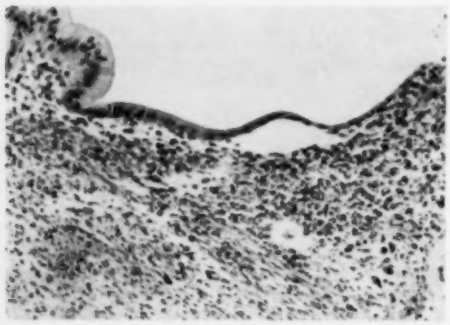

FIG. 657.—Epithelial film growing over ulcer floor. The partial detachment is an artefact. H. and E. (× 85.)

FIG. 658.—Healed ulcer in guinea-pig stomach on twenty-third day. Note the development of simple glands. H. and E. (× 26·5.)

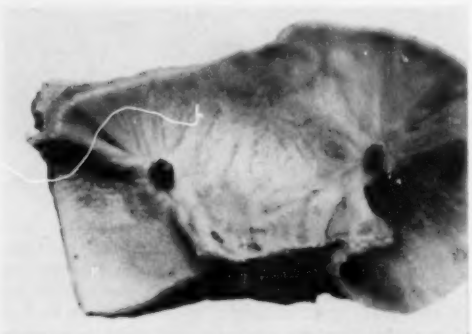

FIG. 659.—Healed gastric ulcers with protruding linen thread which had been incorporated into the floor. (× ⅓.)

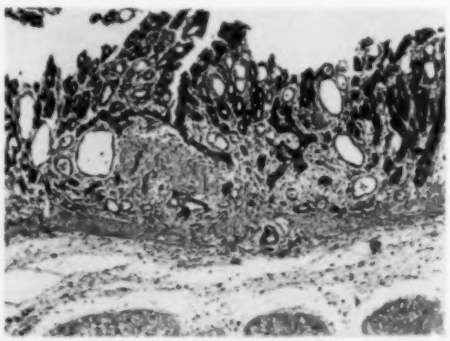

FIG. 660.—Healed erosions in gastric mucosa of guinea-pig given twice daily injections of histamine for 12 days. H. and E. (× 53.)

Mechanical Irritation.—Except for slight interruption of the regenerated mucosal surface by protruding thread, there was no impediment to the healing of the experimental ulcers by incorporated linen or silk suture material (*Fig.* 659).

Hydrochloric Acid.—There was complete healing of the experimental gastric ulcers in all the guinea-pigs given intramuscular injections of the

long-acting histamine preparation for 17 days. As anticipated, however, scattered small histamine erosions and ulcers were present elsewhere in the stomach lining (*Fig.* 660). Some of these were acute, others healed or healing.

There was also complete healing of the gastric ulcers produced in the guinea-pigs with a 'wasp-waist' stomach at the end of the 17-day period, also in those ulcers which were produced within gastric pouches.

Alcohol.—Only 12 out of the 30 animals survived the full 17 days of the experiment; these were emaciated and had lost a quarter to a third of their body-weight at the commencement of the experiment; the body fat was small in amount and dull yellow-brown; the large intestine was distended with firm, dry, brown, scybalous fæces; the adrenals were enlarged and the thickened cortex dark brown in colour; the liver was about normal or slightly smaller than normal in size and dark brown, and microscopically it showed slight fatty change.

In all the survivors there were many erosions and ulcers in the stomach. Microscopically, these presented acute or subacute inflammatory features, often severe, but no notable chronic inflammatory signs; *Fig.* 661 is characteristic of many of these lesions. Variable degrees of glandular degeneration, atrophy, and disappearance, associated with changes in the surface epithelium suggestive of healed erosion, were present in other parts of the stomach mucosa. Despite the widespread nature of these erosions and ulcers the 'cautery' ulcer had healed completely in 4 animals (*Fig.* 662); in 2 more animals healing was complete except for a minute central deficiency;

FIG. 661.—Ulcerated portion of stomach in guinea-pig given 60 per cent alcohol 48 hours previously. H. and E. (× 40.)

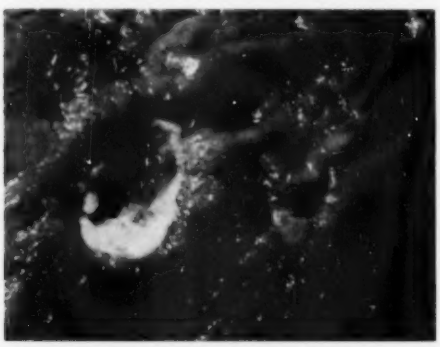

FIG. 662.—Part of stomach of guinea-pig given 60 per cent alcohol for 17 days showing (*a*) a large acute 'alcohol' ulcer on the left, and (*b*) a healed 'cautery' ulcer on the right. (× 6.)

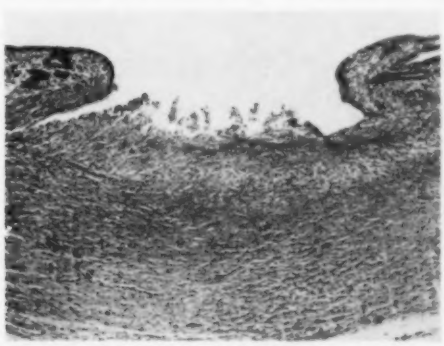

FIG. 663.—Unhealed 'secondary' ulcer on seventeenth day. H. and E. (× 40.)

FIG. 664.—Unhealed ulcer produced by 'external' ring burn. Day 17. (× 4.)

FIG. 665.—Section of the ulcer shown in *Fig.* 664. H. and E. (× 30.)

in 6 animals there was an unhealed central area 1·5–2·0 mm. in diameter, with microscopical appearances of subacute ulceration, while erosions were present in the immediately adjacent mucosa.

Secondary Ulcers.—After 17 days complete healing of the small acute ulcers produced on the site of healed large ulcers had occurred in only 4 of the 16 surviving animals. In the remaining 12 animals the small ulcer was unhealed and chronic in its histological appearances, with a thick, densely fibrous floor and no epithelial covering (*Fig.* 663).

'Ring Burns'.—Ring burns on the mucosal aspect of the stomach did not affect the normal healing of 4-mm. ulcers, but in the 10 animals in which the burns had been produced on the serosal aspect of the stomach there was marked retardation of healing in 5 animals, moderate retardation in 3 animals, and normal healing in only 2 animals. Unhealed ulcers are illustrated in *Figs.* 664 and 665. The ulcer floor is densely fibrous and there is an obvious lack of an epithelial covering.

Local Injections.—

Freund's Adjuvant.—In the 8 surviving guinea-pigs killed after 30 days of the experiment, the ulcers which contained this adjuvant in their floor were all unhealed. The ulcer base (*Figs.* 666, 667) was composed of loose granulation tissue containing numerous vacuolated and granular histiocytes, lesser numbers of polymorphonuclear leucocytes, and some oil spaces. Acid-fast bacilli were also present both extracellularly and also within histiocytes. The ulcer floor was thick but the amount of collagen present was relatively slight. In all the ulcers there was some epithelial covering, but in only 2 of them was it nearly complete; the new epithelium, which was cubical or columnar and degenerate-looking, was very loosely attached to the underlying inflammatory tissue and was easily detached.

FIG. 666.—Part of an unhealed gastric ulcer injected with Freund's adjuvant. H. and E. (× 30.)

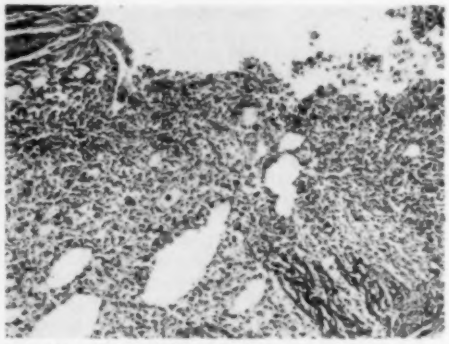

FIG. 667.—Detail of the floor of an unhealed gastric ulcer injected with Freund's adjuvant. H. and E. (× 90.)

FIG. 668.—Healed gastric ulcer injected with Bayol F. Note the large oil spaces in the floor. H. and E. (× 30.)

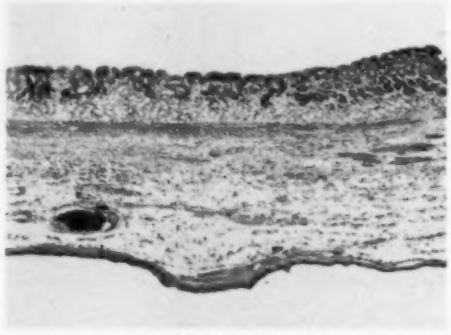

FIG. 669.—Completely healed gastric ulcer 30 days after the local injection of 1 per cent carrageenin. H. and E. (× 30.)

Mineral Oil alone.—Of the 9 animals surviving the 30 days of the experiment, complete healing of the ulcers which contained the mineral oil in the floor was present in 7. Microscopically (*Fig.* 668), the scar was a thin one. The regenerated mucosa was well formed and rested on a substrate composed of fibrous connective tissue containing some prominent oil spaces; the latter were associated with a mild histiocytic reaction. In the remaining 2 animals healing of the ulcer was complete except for a minute central area where there was some dense fibrous tissue, accompanied by a foreign-body reaction, and absent epithelium.

Mixture of Mineral Oil and Emulsifying Agent.—In the 7 animals which survived the 30 days of the experiment, there was complete healing of the large gastric ulcer containing this mixture in its floor. The histological appearances resembled those seen after

the injection of mineral oil alone, but the histiocytic reaction and the degree of fibrosis were slightly greater.

Carrageenin.—At the end of the 30-day experiment the gastric ulcers produced at the site of injection of carrageenin were completely healed in the 8 surviving animals. The regenerated mucosa was well formed and rested on a base which consisted not of dense fibrous tissue but of finely-textured fibro-fatty connective tissue (*Fig.* 669).

B.C.G. Vaccine and Tuberculin.—There were 8 survivors in the experiment in which B.C.G. vaccine had been injected into the stomach wall of 12 guinea-pigs. In all the animals the injected site presented a granulomatous reaction with numerous large mononuclear cells and smaller numbers of polymorphonuclear leucocytes, many acid-fast bacilli, and a variable, but generally slight, amount of collagen. In 2 animals a defect remained uncovered by epithelium (*Fig.* 670), but in the other 6 animals there was complete covering by epithelium; the latter appeared to be firmly adherent to the underlying granulation tissue, which was, however, less in amount than in the uncovered ulcers.

FIG. 671.—Unhealed gastric ulcer associated with the local injection of ferrous sulphate. (× 5.)

In all the animals in which tuberculin had been injected into the stomach wall after preliminary sensitization by intramuscular injection of B.C.G. there was complete healing of the experimental gastric ulcers, with no abnormal features.

Ferrous Sulphate.—At the end of the 17 days of the experiment, when normally, a 4-mm. gastric ulcer should have healed, there was incomplete healing in 4 animals at the site of injection of ferrous sulphate (*Figs.* 671, 672). Microscopically, the fibrous floor contained numerous siderocytes and was covered by a thin layer of granulation tissue and purulent exudate. In the other 6 animals healing was complete; in these ulcers only a few siderocytes were present.

'Gastrostomy Ulcers'.—As already mentioned, the technique employed in these studies for producing gastric ulcers requires opening of the anterior wall of the stomach. After the ulcer has been produced on the posterior wall, the gastrostomy opening is closed by a purse-string suture, using linen thread. It was observed that an ulcer almost always developed at this gastrostomy site and its appearance after 3 weeks closely resembles that of a human chronic ulcer (*Fig.* 673). The ulcers are prominent lesions of variable size and shape, some round and at least 2 mm. in diameter, while others are oval or pear-shaped and up to as much as 12 mm. in length; a small minority are irregularly shaped. They are usually deep, with a floor which is firm and fibrous, but covered by a narrow purulent and necrotic layer. Suture material protrudes from the mucosal surface of some, but in others such material has entirely disappeared. Firm fibrous adhesion of the ulcer to the overlying liver is a common finding. Microscopically (*Fig.* 674), the floor is remarkably like that of human chronic gastric or duodenal ulcers: beneath the surface layer of purulent and necrotic material there is a layer of vascular connective tissue which merges, in the deeper part of the ulcer, into densely collagenous tissue containing only a few blood-channels and no muscle-bundles. The mucous membrane immediately around the ulcer shows

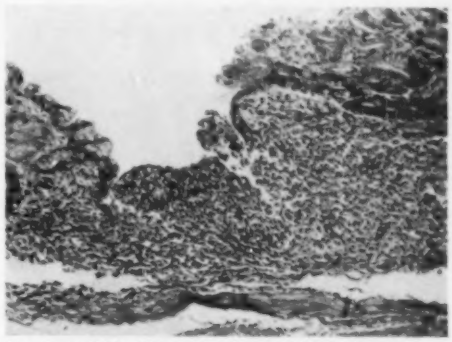

FIG. 670.—Unhealed gastric ulcer associated with the local injection of B.C.G. H. and E. (× 90.)

FIG. 672.—Section of the ulcer in *Fig.* 671. H. and E. (× 30.)

regenerative signs, another point of resemblance to the human counterpart. In contrast to the human variety of chronic gastric ulcer, lymphocytes and plasma cells are absent.

DISCUSSION

There is a consensus of opinion that two factors are concerned in the causation of chronic peptic ulcers: (1) The primary factor responsible for the initial trauma; and (2) The secondary factor which interferes with the normal healing process. Beyond this simple statement, however, the medical literature abounds with conflicting ideas and it is obvious, even on clinical evidence alone, that there is still a great deal to be learned about the gastro-intestinal tract in this respect. At first glance there appear to be overwhelming reasons why HCl-pepsin should be considered of prime aetiological importance in human pathology: the fact that peptic ulcers occur only in these parts of the alimentary tract bathed by gastric juice; the fact that these ulcers are rarely encountered when achlorhydria is present; and, lastly, the fact that prolonged achlorhydria is associated with cure. However, while it can be admitted that some acute peptic erosions and ulcers may be caused by gastric juice, particularly in the intestine, there are many reasons why factors other than HCl-pepsin must be at least equally important, if not more so, in the pathogenesis of *chronic gastric* ulcer: in many patients with this disease the acid secretion is subnormal and even close to achlorhydria; the lesions are focal and often solitary; acute gastric erosions and ulcers normally heal completely and quickly; moreover, experimental acute ulcers heal in spite of a sustained hyperchlorhydria; finally, in both human and experimental chronic gastric ulcers, evidence of digestion of the ulcer floor is inconspicuous.

It would seem that in the past undue emphasis has been placed on the acid pepsin factor and too little attention focused on protective factors; the latter have been studied much less and are little understood.

FIG. 673.—A large chronic ulcer on the mucosal surface of the anterior wall of a guinea-pig stomach at the site where the organ was incised and sutured 23 days previously. (× 1.)

Doubt concerning the prime importance of acid in the aetiology of chronic peptic ulcers has already been expressed by a few investigators, e.g., Oliver (1949) and Appleby (1948). Moreover, James and Pickering (1949) believe that the acid factor is operative in duodenal ulcer but not in gastric ulcer. They made 24-hour observations on the gastric acidity in 20 cases of duodenal ulcer, 23 cases of gastric ulcer, and 20 controls, and they found that subjects with duodenal ulcer yielded more and subjects with gastric ulcer less HCl per hour than normal subjects. They deduced that gastric and duodenal ulcer are essentially distinct disorders and that the chief agent in their pathology is different, also that there is something other than intragastric acidity which is the essential agent in the pathogenesis of gastric ulcer.

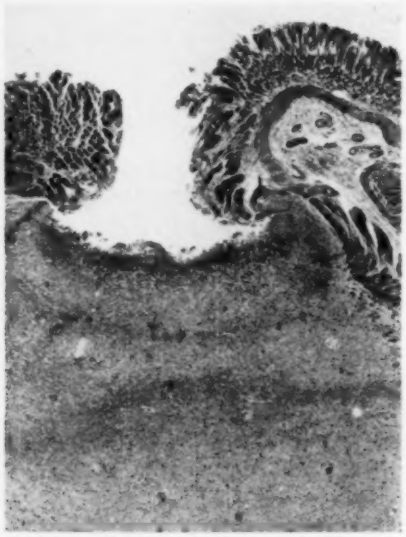

FIG. 674.—Section of the ulcer shown in *Fig.* 673. H. and E. (× 16.)

The idea that peptic ulcer is probably not the result of any simple group of aetiological factors has been expressed by Card (1952), Smith and Rivers (1953), and Dempster (1957). Card has written: "... it is most unlikely that peptic ulcer has a single universal cause ... there are likely to be multiple causes, any one of which may be operating at one time or in one place; the cause of ulceration in the Southern Indian peasant is not necessarily the same as that of the London stockbroker; perhaps in searching for the cause of ulcer we should emphasize this by asking our question the other way, 'Why do people not get ulcers?' "

Most people agree that an area of devitalization of tissue precedes ulcer formation and some of our predecessors have recorded their observations and conceptions by using the term 'locus minoris resistentiæ', but such erudition has concealed their ignorance of the essential mechanism involved. It certainly seems reasonable to assume that chronic peptic ulcers arise from acute ulcers or possibly

erosions. Ivy, Grossman, and Bachrach (1950) have aptly expressed the situation thus: "It is difficult to conceive, and no-one has explained adequately how a chronic ulcer could arise, like Minerva springing fully armed from the forehead of Jove, without it being an acute lesion of the mucosa." Acute erosions are common lesions in the stomach and acute and subacute gastric ulcers are also well recognized. These lesions are caused by a wide variety of agents (Selye, 1951; Ivy, Grossman, and Bachrach, 1950); normally, the lesions heal rapidly, but, for reasons that are not entirely clear, they develop into chronic ulcers in certain subjects. Since Virchow's time vascular disease, including spasm, has been frequently proposed as the initial cause of erosions and ulcers, and in this connexion it is of interest that Schindler and Baxmeier (1939) noted hæmorrhagic erosions in the gastric mucosa of 44 per cent of patients with gastric ulcer as compared with only 5·6 per cent without gastric ulcer; this observation lends support to the view that a localized vascular disorder, e.g., vasospasm, produces an acute erosion or ulcer which may progress to form a chronic ulcer. Experimental support for the importance of blood-supply in the development of chronic gastric ulcers has been mentioned earlier in this paper: chronic gastric ulcers developed following external ring burns of the stomach wall. Normal healing was associated with internal ring burns presumably because the blood-supply to the ulcer remained adequate for healing, whereas the external ring burns substantially reduced the blood-supply by injuring large subserosal vessels.

There is very little evidence that gastritis is a cause of chronic gastric ulcers in humans; even extensive chronic inflammatory lesions (*Fig.* 675) may be associated with an intact mucous membrane. Animal experiments described here, using tubercle bacilli and tuberculin, also demonstrate that injection as a cause of chronicity in gastric ulcers is not of fundamental importance. The roles of many other possible factors, such as endocrine or nervous influences, are still undetermined.

Descriptions have been given of experiments in which chronic gastric ulcers developed in animals: (*a*) where a second ulcer was produced at the scarred site of a former, larger ulcer; (*b*) when an external ring burn was produced around a gastric ulcer; (*c*) following the local injection of 'irritants' such as Freund's adjuvant or ferrous sulphate; and, finally, (*d*) at sutured gastrostomy sites. In all these instances there was a failure of the growing epithelium to cover and adhere to the ulcer floor, which was either densely fibrous or loose and irregular. It is deduced, therefore, that a special study of factors influencing the adherence of epithelium to underlying connective tissue is likely to prove of great value in our understanding of the peptic ulcer problem and, indeed, in other types of chronic ulcer. In 'callous' ulcers of the skin the histological appearances are essentially similar to those of chronic peptic ulcers, and in these lesions there is the same failure of epithelium to cover a dense fibrous floor.

Aschoff (1924) believed that chronic gastric ulcers in humans developed from erosions if the latter were present on the lesser curve, and he suggested that the reasons for this sequence were the lack of mucosal mobility and the discharge of chyme along the lesser curve, and possibly also muscle spasm. No one has adequately explained the cause of the peculiar localization of chronic gastric ulcer to the lesser curve region. Possibly local anatomical factors are important, but the detailed observations of Barlow, Bentley, and Walder (1951) give no support to the contention that there is a deficiency of blood-vessels in this region; moreover radiographic evidence (Neilson and Christiansen, 1932; Gianturco, 1934)

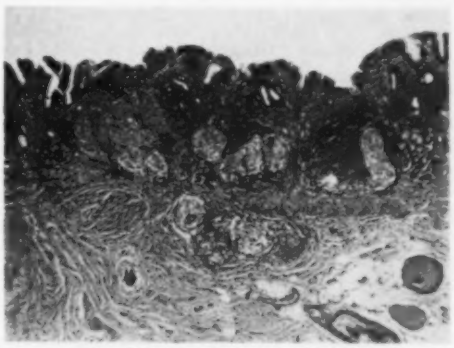

FIG. 675.—Sarcoid lesions in mucosa and submucosa of human stomach. Partial gastrectomy specimen. H. and E. (× 26·5.)

indicates that there is, in fact, very little traffic, if any, along the *Magenstrasse*, which appears to be more of a hypothetical pathway suggested by the anatomical appearances. In any case, it seems that the role of mechanical trauma, e.g., by hard food material, in producing chronic gastric ulcers in humans has been grossly exaggerated. As already described, chronicity could not be induced in experimental ulcers by incorporating suture material in the floor. In relation to dietary factors, it is also of considerable interest to observe that an experimental ulcer can still heal normally despite the daily administration of a large quantity of concentrated alcohol into the stomach.

SUMMARY

1. Two components are involved in the healing of a gastric ulcer: (*a*) epithelial growth; and (*b*) growth of connective tissue.

2. Attempts have been made to inhibit the healing of acute gastric ulcers produced by a standardized cautery method in guinea-pigs.

3. Chronicity results if the nature of the ulcer floor precludes the adhesion of growing epithelium over it, e.g., if the floor is densely fibrous and avascular or if it is very soft and uneven. There is a suggestion that local vascular impairment may be a critical factor. There is no proof that hydrochloric acid of itself is the cause of chronicity.

4. Further studies on factors determining the adhesion of epithelium to connective tissue may be of considerable value in the problem of chronic peptic ulceration.

This paper is part of a Ph.D. thesis accepted by the University of Edinburgh. My sincere thanks are due to Professor G. L. Montgomery for his interest and assistance, and to all who have given technical help, particularly Mr. T. C. Dodds.

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SHORT NOTES OF RARE OR OBSCURE CASES

A CUTANEOUS HORN OCCURRING IN THE THIGH

REPORT OF A CASE

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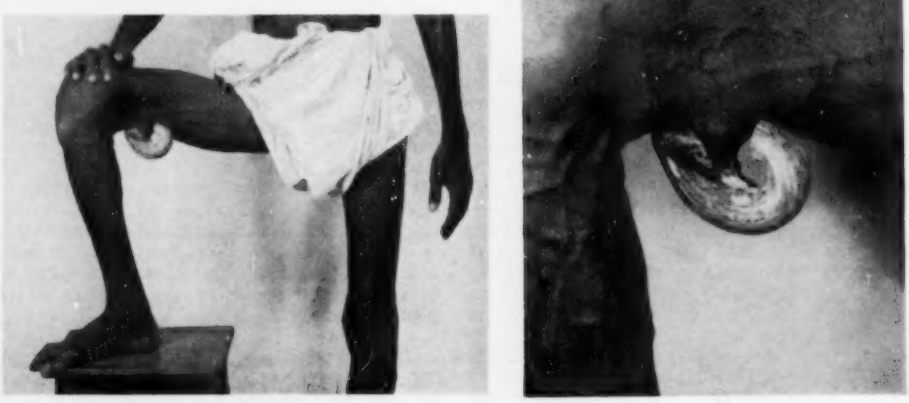
CUTANEOUS Horn or Cornu Cutaneum is a characteristic localized keratinous outgrowth from the epidermis.

Ormsby and Montgomery (1954) doubt whether many of the cases of cutaneous horn reported in the literature are in fact true epithelial outgrowths. Horns can also arise from sebaceous cysts, verruca vulgaris, and filiform papillæ, associated with poor skin hygiene. This may explain the comparative infrequency of carcinomatous change (12 in Montgomery's series of 83 cases and 10 per cent in Leverth's series) because a true epithelial horn is almost always accompanied by a precarcinomatous senile keratosis of the base with prolongation of the rete pegs into the cutis and hypertrophy of the papillary bodies. The horn may arise secondary to a malignant degeneration, but only very rarely.

Cutaneous horns are seen more often in women, and the most common areas are the face, scalp, and hands. An illustration in Bailey and Love's *A Short Practice of Surgery* depicts a widow called Dimanche who sold watercress in Paris. She had a slender horn



A B

FIG. 675.—A, The exact situation of the horn is seen. It used to rub against the inner side of the left thigh when he walked. B, A close-up of the horn shows its resemblance to a ram's horn.

growing from her forehead. The buttocks and the male genitalia are less common sites.

The pathological changes at the base of the horn depend on the underlying cause. There may be a senile keratosis, or any hyperkeratotic lesion like arsenical keratosis, warts, clavi, callus, ichthyosis, sebaceous cysts, or even an incompletely closed epithelial inclusion cyst. The horn itself shows a dense hyperkeratotic stratum corneum with scattered areas of parakeratosis.

FIG. 677.—Plain radiograph demonstrating the outline of the horn.

CASE REPORT

V., a 55-year-old male, a peasant by occupation, was admitted in July, 1958, with a history of dyspepsia and vomiting. He was suspected to have a duodenal ulcer causing pyloric obstruction. Laparotomy showed a stenosing ulcer in the first part of the duodenum for which a posterior gastrojejunostomy was performed.

Incidentally he had a rough horn growing from the back of the lower third of his right thigh. It started three years ago as a round hard callosity, and gradually developed into a horn. A year back there was some ulceration of the overlying skin, with a foul-smelling discharge. Recently the horn had begun to interfere with his gait and he had had to trim it every two months. It was quite painless. No one else in his family had a similar condition.

The horn was about 6 in. long, and was a hard, chitinous, cylindrical outgrowth coiled to about three-quarters of a turn, the broader end being attached by a heaped-up mass of horny material to the skin of the posteromedial aspect of the lower third of the right thigh, the narrower end being truncated and directed upwards and medially. It showed the linear grooves and ridges typical of a horn. Its base could be moved painlessly over the muscles and deep fascia (*Fig.* 676). The inguinal nodes were clinically normal. The outline of the horn could be seen in the plain radiograph, but there was no bony involvement (*Fig.* 677).

The horn was excised with a margin of healthy skin around it. On histological examination the horn showed laminæ of deeply staining keratinized cells. The skin at the base showed hypertrophy of the papillæ with round-cell infiltration. There was no evidence whatever of malignancy (*Fig.* 678).

The operation wound healed in two weeks, after which the patient was discharged from the hospital. He reported for follow up eight months later. The wound had healed well and there was no recurrence. The inguinal nodes were normal.

FIG. 678.—Histophotograph of the horn, showing characteristic concentric whorls of flattened cells as well as keratin fibres.

SUMMARY

The presence of a large cutaneous horn of the lower third of the right thigh in a patient with duodenal ulcer is recorded. The incidence and pathological features of cutaneous horn are discussed.

Acknowledgements.—We are grateful to the Dean, Government Stanley Medical College, Madras, for permitting us to report this case.

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A SUBCLAVIAN ARTERY AS THE MEANS OF BLOOD-SUPPLY TO THE LOWER HALF OF THE BODY

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AMONG the patients whose abdominal aneurysms have been resected at the Royal Perth Hospital is one in whom the bursting of the aneurysm and disruption of the proximal aorta were so extensive that the usual operative measures were not feasible. The story seems to deserve a brief record.

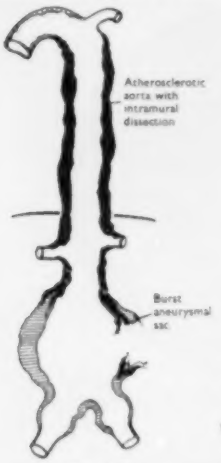

FIG. 679.

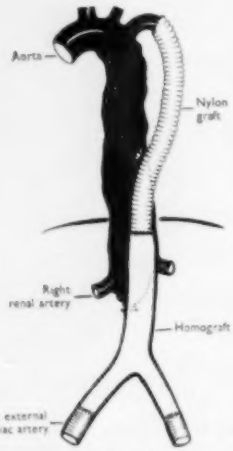

FIG. 680.

FIG. 679.—The aneurysmal disruption and aortic dissection.
FIG. 680.—The nylon graft and homograft in continuity.

CASE REPORT

George L., a greenkeeper, aged 53 years, entered hospital on Aug. 4, 1959. He said: "Twelve hours ago I felt a dull pain in the lower part of my abdomen. It lasted several hours, spreading upwards to the small of my back. The pain reappeared after an interval of three hours and has since gradually become worse. Otherwise my health has always been good and I do not recall any previous serious illness or accident." His appearance was that of health. Arterial pressure was 170/100 mm. Hg and pulse-rate 78 a minute. Pulsations of arteries in the limbs were easily perceptible and peripheral circulation was adjudged normal. In the abdomen to the left of the umbilicus was a pulsating oval mass, duck's egg in size: it was not tender.

In the evening of the following day the pain suddenly increased. He perspired and his pulse-rate rose to 90 a minute: arterial pressure fell to 80/50 mm. Hg. On transfer to the University Department of Surgery blood was infused intravenously and hypothermia induced: then his abdomen was opened by an anterior longitudinal incision. Much blood had extravasated behind the peritoneum, and clearance of the clot revealed a widely disrupted aneurysm, involving the aorta below the left renal vein and including the common iliac arteries. In addition to the tearing of the sac, there was dissection of the aorta proximally as far as could be seen, the circumference of the blue vessel being greatly increased. The aneurysm was excised.

An attempt to reconstruct the end of the aorta failed owing to the degree of intramural dissection and the calcareous condition of the atherosclerotic inner coat. Inspection of the vessel at, and above, the renal arteries and also above the pancreas showed no improvement, so the left side of the chest was opened. The thoracic aorta was similarly dilated, discoloured, and unsuitable for anastomosis. At the arch of the aorta the dissection faded away to reveal intensely atherosclerotic aortic wall (*Fig.* 679). It was confirmed that the dissection had not started at this level and hence probably originated from the site of aneurysmal disruption. The degree of atherosclerosis at the arch was such that again no part of the wall was thought suitable for anastomosis. The middle third of the left clavicle was removed and at last a vessel suitable for the attachment of a graft, the left subclavian, was exposed. After division of the artery and ligation of its distal end, the proximal end was united with the longest graft available—of ⅜-in. crimped nylon. The free end of the graft was passed subcutaneously down the front of the thorax to appear in the abdomen just to the left of the xiphoid process. There it was in turn grafted into an aortic and common iliac homograft, the distal ends being joined, end to end, to the left and right external iliac arteries about 2 in. above the inguinal ligament (*Fig.* 680). The internal iliac arteries, being atherosclerotic and almost occluded by thrombus, were ligated.

His post-operative course was not remarkable. Blood-urea was 31 mg. per cent on the day after operation, rose to a zenith of 302 mg. per cent on the fifth post-operative day, and fell to normal by the fourteenth day. Liver-function tests stayed normal, as did serum-proteins and blood-calcium. There was no change in the electrocardiograph pattern. Three weeks after operation anticoagulatory preparations were prescribed and have been continued since.

Two months after leaving hospital he reluctantly admitted his willingness to resume work and has continued since in his occupation as a greenkeeper, a particularly arduous job in the hot summer weather here. At first there was a feeling of tightness across the chest in certain bending postures. He also noticed a 'frozen feeling' in the right buttock if he walked fast for a distance of more than one hundred yards: by avoiding this degree of exertion he has been able to perform all his usual activities without discomfort. His appetite has remained good and weight has been gained.

There is a thrill at the subclavian anastomosis and a bruit which diminishes along the graft to disappear in the lower chest. There is no abdominal mass, thrill, or bruit. All pulses are palpable in the lower limbs. Both upper limbs are normal, apart from the absence of pulses in the left. Temperatures in arms and legs vary within 4° only, except for an unexplained and symptomless drop of almost 8° distal to the middle of the calf of the left leg which has persisted since operation. Eighteen months have now passed since his illness and he is seen to be well when he calls periodically for routine checking of blood coagulability.

The grafting procedure was adopted to save his life in an emergency, and was done with the recognized possibility of a more orthodox method being required when the tissues involved in the aortic dissection had organized. The double graft is unaided substantially by flow through the lumbar arteries in supplying the lower half of the body since most of these were thrombosed before, or ligated during,

operation. The continued well-being of the patient has invalidated further operation.

SUMMARY

This is a short account of a patient whose abdominal aneurysm burst with extraperitoneal blood-loss and massive intramural dissection to the arch of the aorta. A crimped nylon graft and a freeze-dried homograft were used in continuity to restore blood-supply to the lower half of the body by way of the left subclavian artery, with distal anastomosis to the external iliac arteries.

COMPLETE RUPTURE OF THE PANCREAS

By D. W. BRACEY, Peterborough

The rarity of rupture of the pancreas as an isolated non-penetrating injury, there being only 21 cases recorded up to September, 1959, raises the question of the mechanism of this unusual injury. In recording the following case—the twenty-second of complete rupture—a suggestion as to its causation is made, together with an outline of a new treatment which might be applicable in future instances.

CASE REPORT

Mrs. J. M., aged 21 years, was a passenger in the bucket seat of a sports saloon which skidded and turned over on its back. She remembered clearly gripping the sides of the seat and holding herself in a flexed position throughout the skid and the turnover. She was not rendered unconscious and was extricated from the car, upside down, and still in a flexed position, through the side window. She was absolutely certain that she received no direct blow on her abdomen.

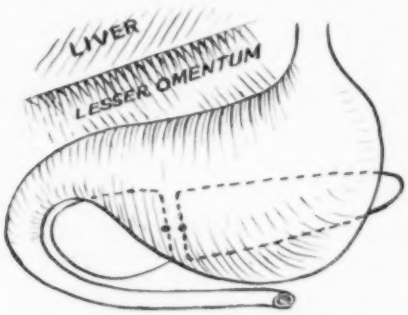

Fig. 681.—Diagram of the operative findings.

On Examination.—The only physical sign was some tenderness, associated with slight pain, in the left hypochondrium. There was no evidence of shock and her pulse and blood-pressure were normal. She had vomited twice before admission, but for the first four days in hospital she enjoyed a light diet and appeared to be in less pain. Radiographs of her abdomen were normal, but a chest film showed some elevation of the left diaphragm. A mild pyrexia from admission continued and a white cell-count revealed a total of 20,900 W.B.C. with a 95 per cent polymorph leucocytosis. Her hæmoglobin was 79 per cent.

On the fifth day she complained of nausea, was apprehensive, but would not admit to any pain. Examination revealed a fullness in the epigastrium and some slight tenderness in the left hypochondrium. A serum-amylase taken this day showed a concentration of 100 Wohlgemuth units (normal 3–10 units), and with a provisional diagnosis of a pancreatic injury, laparotomy was performed the next day—Oct. 4, 1959—seven days after the accident.

Operative Findings.—The stomach was pushed forward by a large collection of fluid (2 pints) trapped in the lesser sac. There were a few scattered areas of fat necrosis in the upper abdomen. After aspiration of the fluid, which was opalescent and very slightly blood-stained, the lesser sac was entered through the lesser or gastro-hepatic omentum to reveal a complete vertical split in the pancreas just to the left of its head. The edges of each portion were hæmorrhagic and the cut ends of the duct were clearly visible (*Fig.* 681).

Procedure.—The body and tail of the pancreas were almost completely mobilized to the left of the split, whilst the head of the gland was left untouched. The anterior and posterior walls of the stomach were then opened in the long axis of the stomach. The body of the pancreas was brought through the posterior incision in the stomach into its lumen and secured to the edges of the incision with catgut stitches, as a pancreatico-gastrostomy. The anterior wall of the stomach was then closed and the lesser sac drained (*Fig.* 682).

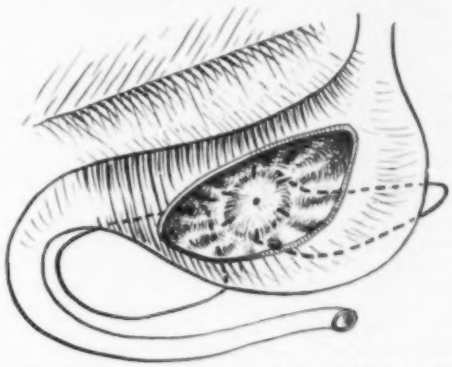

Fig. 682.—Diagram of the approach through the stomach for the pancreatico-gastrostomy. The proximal part of the pancreas was left untouched.

Progress.—Over the first eighteen days post-operatively the drainage tube from the lesser sac drained, in diminishing daily quantities, a total of 1 ⅝ oz. (7·8 pints) of pancreatic fluid, presumably from the head of the pancreas. Her discharge to her home in Birmingham was held up till the thirty-second day because of wound sepsis. On discharge she had completely recovered her appetite, was gaining weight, and had no symptoms.

DISCUSSION

Blandy, Hamblen, and Kerr (1959) give a comprehensive review of recorded cases and a thoughtful discussion as to the mechanism of complete rupture and its treatment. The history in this case leaves no doubt in the writer's mind that there was no direct

blow on the abdomen—in fact, the very flexed position of the patient's body protected her abdomen from a frontal blow. Perusal of the literature reveals that in many cases the direct abdominal injury—where it has occurred—does not seem to have been of sufficient intensity to have caused such a severe injury to such a deep-seated organ. The direction

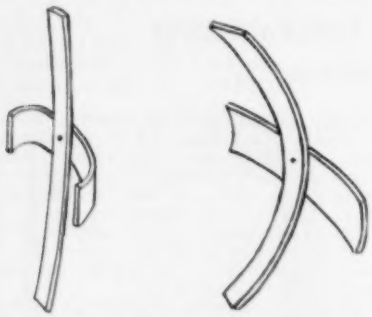

FIG. 683.—Illustrating the effect of bowing a vertical piece of balsa wood (simulating flexion of the spinal column) on a bowed cross-piece fixed to its middle. Flexion of the upright produces a less degree of bowing in the cross-piece (simulating the outward movement of the lower thoracic cage).

(vertical) and site of the split of the pancreas in this case seemed to suggest that the pancreas had been pulled from both ends over a relatively unyielding structure, viz., the aorta.

To obtain these conditions, that is, a pull simultaneously from the head-end and the tail-end of the pancreas, would necessitate postulating that the transverse diameter of the lower thoracic cage underwent a sudden unexpected increase during the accident. If this does in fact occur, then the structures in the retroperitoneal tissues in the upper abdomen will tend to move away from the midline in a lateral direction. Furthermore, any structure lying transversely across the midline in the posterior upper abdominal region will tend, if inelastic and unsupported by a strong capsule, to split at the point of its greatest curvature, i.e., at the junction of the head and the body in the case of the pancreas. The expression 'point of its greatest curvature' is used to emphasize that anatomically the pancreas does not just lie transversely across the upper abdomen behind the lesser sac, as necessarily depicted in textbooks, but is disposed rather like a 'comma' reversed and lying horizontally. The short, sharply curved end of the comma represents the head of the pancreas and the long, less sharply curved part the body and tail. In the horizontal plane of the body at this level the head of the pancreas lies near the side of the spinal column and comes forward to arch over the aorta as the neck of the pancreas, whilst the body curves backwards in a posterolateral direction ending in the tail of the pancreas just behind the anterior plane of the spinal column.

To simulate what happens when the spine becomes acutely flexed (as in this case) or when it becomes reflexly bent in response to a fairly heavy blow in the abdomen (the victim 'doubling up'), an apparatus was set up as follows (*Fig.* 683): Two pieces of 3-in.-wide balsa wood, one 3 ft. long and the other 2 ft. long, were fixed together in the centre in the form of a cross. The vertical longer piece represented the spine and the shorter transverse one (shaped into a bow after steaming) the lower thoracic cage. If the vertical piece is then bent in a forward curve (to represent flexion of the spine) then the transverse piece will be seen to undo its bowing and its ends move away from each other. When the vertical piece is straightened again the transverse resumes its original curve.

It is therefore suggested that when the human trunk is forcibly flexed the anteroposterior diameter of the thoracic cage shortens and of necessity the transverse diameter increases. This change is more marked on the free or unattached ribs—namely, the lower ones—and thus their ends tend to move away from the midline. The underlying peritoneum in their vicinity and the associated and partially or wholly retroperitoneal organs will be subjected to a pull outwards on each side of the midline.

Thus it is contended that an isolated injury to the pancreas could occur as a result of one or other of the following mechanisms: (1) A crushing blow directly on the upper abdomen; (2) a light blow accompanied by 'doubling-up' action; (3) sustained and accentuated flexion of the trunk (as in this case).

Treatment.—The consensus of opinion as to the treatment of this rare injury has been either excision of the distal portion of the pancreas, or allowing formation of a pseudocyst and then performing a cyst-gastrostomy. In the case presented, the distal portion represented at least three-quarters of available pancreas, removal of which might have proved detrimental to the future health of the patient. The policy of cyst-gastrostomy entails a second operation after an interval which might well be a stormy one for the patient. At operation in this case it was realized that the secretion which would inevitably leak from the head of the gland would cease in a matter of one to three weeks, so it was decided to conserve the distal and major portion of the organ by performing pancreatico-gastrostomy. Post-operatively the presence of pancreatic ferment in the stomach was proved, but an attempt to outline the pancreatic duct draining into the stomach with gastrographin was unsuccessful.

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MULTILOCULAR CYST OF THE GALL-BLADDER

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ANOMALIES of development in the human gall-bladder are rare. Boyden (1926), in his study of the morphology of accessory vesicles of the gall-bladder, was only able to find 20 cases in the literature up to 1926. Furthermore, he was able to collect no more than 5 examples from reports of over 19,000 patients and cadavers.

FIG. 684.—Anterior view of the specimen, showing the gall-bladder stretched over the underlying cyst.

Lockwood (1948), in a review of 1464 consecutive cholecystograms, found 41 cases of congenital deformities of the gall-bladder—a considerably higher incidence than was found by Boyden.

Neither of these authors records a cystic abnormality in this region, and, indeed, such reports are very scarce. Feldman, Goodman, and Weinberg (1942) describe a small mucosal cyst in the fundus of the gall-bladder in association with varices of the cystic veins, and Furnival (1950) describes a similar cyst which produced a filling defect on cholecystography. Rabinovitch, Rabinovitch, and Zisk (1956) report the case of a man, aged 62 years, in whom a cyst containing gall-stones was found lying between the right hepatic duct and the gall-bladder. In this case the left hepatic duct opened directly into the duodenum. Bishop (1901) described a case closely resembling the present one. However, in his specimen the gall-bladder was absent, and the pedicle of the tumour was formed by the cystic duct.

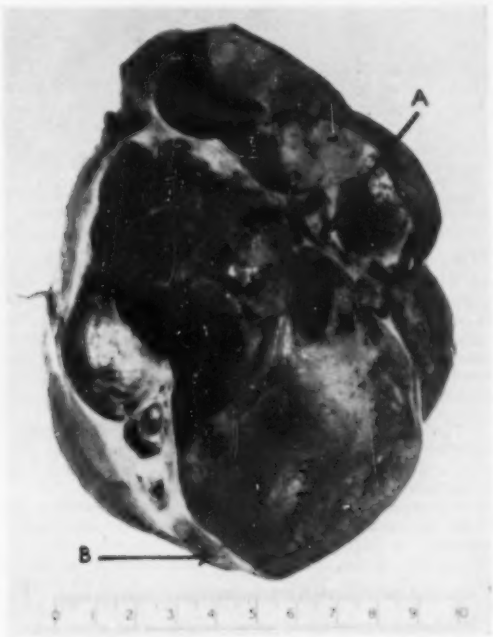

FIG. 685.—The anterior half of the multilocular cyst viewed from behind. The section illustrated in *Fig.* 686 was removed from site A. The tip of the gall-bladder can be seen at site B.

The occurrence of a large multilocular cyst in association with an anatomically normal gall-bladder appears to be unique in the literature.

CASE REPORT

HISTORY.—The patient (Mrs. J. D.) was a housewife, aged 71 years. Two days before admission she had complained of slight nausea and anorexia. The following day she noticed for the first time a large swelling in the right hypochondrium. There was no history of dyspepsia, fat intolerance, or jaundice; bowel function was normal, and there were no symptoms referable to the urinary system.

Past History.—Four years previously, a right femoral herniorrhaphy had been performed at the same hospital. No record was made of any abdominal tumour at that time.

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ON EXAMINATION.—She was rather a frail old lady, but did not look ill. There was no sign of jaundice at the time of admission.

In the abdomen a large lobulated mass was palpable, extending below the right costal margin to the level of the umbilicus. It was continuous with the liver, and moved freely on respiration. It could not be displaced into the loin, and was not tender to deep palpation.

No pre-operative radiographic studies were performed, and it was decided to proceed to laparotomy without delay.

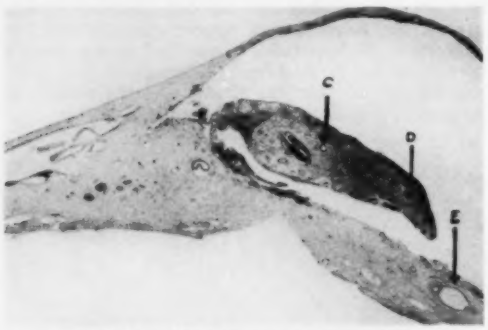

FIG. 686.—A section from one of the cysts in *Fig.* 685, showing a portion of aberrant liver tissue at D. Aberrant bile-ducts are seen in several places, including C and E. Some are considerably dilated. H. and E. (× 5.)

AT OPERATION (Mr. R. S. Corbett).—The abdomen was explored through a right paramedian incision. On opening the peritoneal cavity, a lobulated, cystic tumour was found lying between the gall-bladder and the inferior surface of the liver. The gall-bladder and cystic duct were stretched over the surface of the cyst, but the common bile-duct and hepatic ducts were on its deep aspect hidden from view, making adequate exposure of these structures impossible.

The cystic duct was divided, and the whole mass, together with the gall-bladder, was separated from the liver and removed without difficulty. The wound was closed with drainage.

PROGRESS.—A biliary fistula developed along the track of the drain, and bile continued to leak from this intermittently for four months. A sinogram showed complete obstruction of the common bile-duct below its junction with the fistulous track. The opaque medium passed freely upwards into the hepatic ducts, which appeared normal.

It was therefore decided to implant the fistula into the duodenum. This was successfully performed four months after the original operation. Further progress was satisfactory. When last seen, the patient was very well, with no sign of biliary obstruction.

PATHOLOGICAL REPORT.—The specimen consists of a slightly lobulated cystic mass measuring approximately 13 × 10 × 8 cm. The gall-bladder and cystic duct are stretched out over the surface of the mass (*Fig.* 684). The gall-bladder contains thick inspissated greenish-yellow bile; its wall is slightly thickened, measuring from 0·2 to 0·3 cm., and its mucosa is somewhat granular. Toward the tip of the fundus some bile-filled cavities, approximately 0·1 cm. in diameter, are present. These resemble the pseudo-diverticula commonly seen in chronically inflamed gall-bladders (*Fig.* 685 B).

The multilocular cystic mass (*Fig.* 685) shows no connexion with these spaces, nor with the gall-bladder or cystic duct. It contains thin, slightly blood-stained serous fluid, with no obvious bile or mucus. The loculi vary considerably in size and in the thickness of their walls. Representative portions from the thicker parts of the septa were taken for histological examination.

Histology.—

1. *Gall-bladder*: Sections of the gall-bladder show a mild grade of inflammatory change, with infiltration of chronic inflammatory cells—mainly plasma cells, lymphocytes, and mononuclear histiocytes. Throughout the wall there is cellular fibrous tissue of recent origin, and at several places, particularly at the tip of the fundus, irregular downgrowths of epithelium are found, forming the so-called 'sinuses of Ashcoff and Rokitansky'.

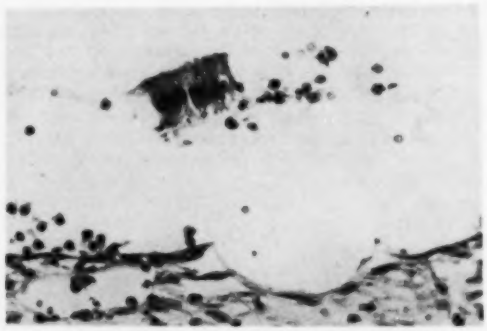

FIG. 687.—A cellular clump lying free in the cyst cavity and adjacent to its wall. H. and E. (× 250.)

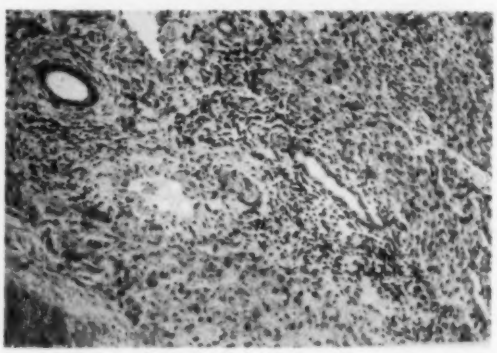

FIG. 688.—Shows liver-cell columns, on the right, and several small hepatic bile-ducts. This section is a higher magnification of site D in *Fig.* 686. H. and E. (× 80.)

2. *Cystic mass*: Sections of the septa of the multilocular cyst show rather œdematous, loosely textured fibrous tissue in which numerous duct-like structures, lined with low columnar epithelium, are embedded. These structures closely resemble intrahepatic bile-ducts. One section includes a portion of liver tissue which was found in one of the thick septa (*Figs.* 686 and 688). A continuous series of ducts can be traced from this aberrant mass into the adjacent cyst wall. Several of these show considerable dilatation.

The large cavities of the cyst are devoid of epithelial lining, except in two areas where clumps of low columnar cells are lying adjacent to the fibrous wall (*Fig.* 687). These are identical with the cells lining the ducts described above, and in no way resemble the tall pale columnar epithelium of the gall-bladder.

The cyst wall also contains a number of clefts, filled with eosinophilic material. These are considered to be lymph spaces, and do not appear to take part in the formation of the main cystic mass.

DISCUSSION

Because of the extreme rarity of cysts in this region, no satisfactory scheme of classification has been devised. In attempting to determine the probable aetiology of this specimen it was therefore necessary to consider several possibilities.

1. *Neoplastic Cyst.*—A carcinomatous or other malignant tumour was readily excluded in this specimen on histological grounds. Numerous blocks of tissue were studied, and no signs of malignant epithelial tissue were discovered.

A lymphangiomatous origin was more difficult to exclude, particularly as some dilated lymphatics were found in the cyst wall. However, neither the contents of the cyst nor the thick fibrous structure of its septa were suggestive of a lymphangioma.

A true adenomatous cyst was also considered unlikely. There was no evidence of actively proliferating epithelium in any part of the specimen examined.

2. *Parasitic Cyst.*—The only kind of parasitic cyst of these dimensions likely to be found in close relation to the liver would be a hydatid. Neither the contents of the cyst nor the histological features of its wall in any way supported such a diagnosis.

3. *Mesenteric Cyst.*—The possibility was considered that this was a mesenteric cyst. Its position lent support to the view that it might have arisen between the leaves of the mesentery of the gall-bladder. Such a mesentery is, of course, a common enough finding, but a cyst has hitherto never been described in connexion with it.

The histological appearances were not those of a simple serous cyst, and the nature of the contents excluded the chylous variety. An enterogenous type of cyst arising during the development of the gall-bladder was, however, considered possible. Enterogenous cysts in connexion with the mesenteries of the intestine are believed to arise by sequestration of diverticula formed during the early stages of embryonic development. In these cases the epithelial lining of the cyst usually closely resembles that of the adjacent bowel.

The epithelial cells of this cyst did not resemble gall-bladder epithelium, and it was therefore considered unlikely that it was derived from this organ. Nevertheless, the histological appearances suggested that the cyst was in fact of developmental origin, and in the next section the view is presented that it arose from the aberrant bile-ducts of Luschka.

4. *Cyst due to Anomaly of Development.*—In his extensive review of this subject, Boyden (1926) recognized four distinct groups of abnormality of the gall-bladder in domestic mammals and humans, any one of which might give rise to a cystic anomaly adjacent to this organ. The groups are as follows:—

a. Cleft gall-bladders, resulting from subdivision of the embryonic primordium, with free communication between the lobules.

b. Diverticular gall-bladders, arising from the neck of the embryonic organ, and occurring in relation to the 'cyst-hepato-ducts'. These anomalies are found in those species, e.g., ungulates, in which the cystic duct is embedded throughout its length in liver tissue.

c. Ductular gall-bladders, derived as outgrowths from the hepatic ducts, and histologically indistinguishable from the main gall-bladder.

d. Trabecular gall-bladders, formed as vesicular outgrowths from the liver bordering the gall-bladder fossa, and found in cattle. These accessory vesicles adhere to the wall of the definitive gall-bladder, and both structures are covered by a common peritoneal investment. The accessory duct empties directly into the liver substance, and has no direct communication with the true gall-bladder.

At first sight it appears that the cyst described here can have no close aetiological relationship with the congenital abnormalities described by Boyden, but in fact ducts related to the underlying trabecular tissue have been described not only in calves (as in group *d* above) and in cats, but also, as Boyden himself noted, in man. These aberrant structures seem identical with those described by Luschka (1858, 1863). The last author probably described both these anatomical duct-like structures, and also the pathological 'diverticula' which are more popularly associated with the names of Aschoff and Rokitansky. Luschka's descriptions are not clear, however, and the controversy and confusion which has existed both before and after Luschka's publications is fully considered by Halpert (1927a, 1927b), and later reviewed by Robertson and Ferguson (1945).

The sinuses of Aschoff and Rokitansky are now well recognized as a commonly acquired abnormality associated with chronic cholecystitis (King and McCallum, 1931), and occasionally such structures present as well-formed diverticula on the external surface of the gall-bladder. Such diverticula may occasionally be demonstrated radiologically (Lawler, 1952), and the possibility of their giving rise to cysts by obstruction at their necks was considered by Weisel and Walters (1942), King (1953), and by Kammerer (1912). Kammerer described a calcareous cyst, 1½ in. in diameter, which he considered to have been formed in this way.

Although some small pseudo-diverticular structures were noted in the gall-bladder, it is not considered likely that the present specimen has any relation to such acquired abnormalities. These structures appear as irregular downgrowths, lined by a tall columnar epithelium, continuous with the gall-bladder mucosa and, like it, staining palely with eosin and secondarily pigmented by bile. Moreover, they are limited to the wall of the gall-bladder: none is large enough to appear on the external surface, and no communication with the multilocular cyst could be demonstrated.

It seems most likely that the cyst that we have described has originated in aberrant hepatic ducts of Luschka. To support this opinion, we recapitulate the following facts:—

1. The site of the cyst is between the gall-bladder and the liver. This is the commonest region in which to find the ducts of Luschka.

2. Several such ducts are present in the cyst wall, at varying distances from a portion of aberrant liver tissue which was found in one of the septa subdividing the cyst. A number of these ducts are relatively dilated compared with normal intrahepatic bile-ducts.

3. Within the cyst itself, occasional strips of low columnar epithelium are found, either adjacent to

the inner surface of the cyst wall, or lying loosely in the debris contained in the cyst cavities. The cells of this epithelium are identical with those lining the aberrant ducts, and show many differences from the mucosal cells of the gall-bladder.

4. No communication of any kind was found between the cyst and the gall-bladder or extra-hepatic bile-ducts.

SUMMARY

A multilocular cyst of the gall-bladder is described in a woman of 71 years. The rarity of such a cyst is noted. The differential diagnosis is discussed and evidence is presented that this cyst has arisen in the anomalous hepatic ducts of Luschka.

We should like to thank Mr. R. S. Corbett for permission to publish this case; Mr. J. W. Miller for technical assistance; Mr. N. K. Harrison for photographs of the specimen; and Dr. G. Sansom for the photomicrographs.

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REVIEWS AND NOTICES OF BOOKS

Les Tractions Vertébrales. By J. LEVERNIEUX. Pp. 124, with 35 illustrations. Paris: L'Expansion Scientifique Française. 18 NF.

THE author bases his advocacy of his method of treatment of intervertebral disk lesions by spinal traction on about 12,000 cases treated, since 1946, with good result (no pain, full movement, return to normal work) in 60 per cent of lumbar cases and 68 per cent of cervical cases.

By experiments on the cadaver, confirmed by radiographs of the living subject, he shows that a widening of the disk space of up to 1·5 mm. can readily be obtained.

Continuous traction in bed is not favoured because of the concomitant muscular atrophy and the need to wear a spinal support afterwards. The recommended method is intermittent extension, without anæsthesia, on a table fitted with a mechanical distraction apparatus by means of which an elongation of up to 17 cm. is obtained at a rate of 2 cm. a minute. The vertical fibres of the annulus fibrosus and the intervertebral ligaments are tensed, slits in the annulus fibrosus are opened up, the central perinucleolar space is expanded, and minor degrees of disk protrusion are 'sucked back'. Relief of pain is often immediate: if there is no improvement after three or four treatments the method should be abandoned as unsuitable.

The treatment is carried out on the ambulant patient, generally without admission to hospital, but it is emphasized that careful control is essential, and particularly the exclusion of diseases such as tuberculosis and secondary neoplasm. In 1 per cent of cases there have been undesirable sequelæ—increased pain, cauda equina lesions, etc.—fortunately nearly all temporary.

The argument is presented with clarity and there are some excellent illustrations and a good bibliography.

Urology in General Practice. By IAN PARTON, M.B., Ch.B., B.Sc. (N.Z.), F.R.C.S. (Eng.), Assistant Urologist, Auckland Hospital, New Zealand. 8½ × 5 in. Pp. 293 + xii, with 35 illustrations. 1960. London: Butterworth & Co. (Publishers) Ltd. 45s.

IN the welter of general and special subjects of the modern syllabus there is no doubt that the teaching of Urology to undergraduates is often scanty. It may happen that a new practitioner has never even passed a catheter, although in any type of general practice he is sure to meet many urological problems. Mr. Parton's book will be a boon to him and a delight to those who are fortunate enough to have had some practical urological training. It contains all that a general practitioner will need to know, and it is written in attractive style, each chapter headed by an apt quotation from Shakespeare. The text is interspersed with anecdotes, their source being in most instances duly acknowledged. It emphasizes many of the urological principles which have been slow to find acceptance in some quarters—for example, that the bacteriological investigation should generally precede the radiological in urinary tuberculosis and that it is dangerous to pass and then remove a catheter in acute on chronic prostatic retention. There is a misprint here (p. 145), small but important, in the substitution of 'or' for 'on'.

We have few criticisms: Xylocaine Jelly is a good urethral anæsthetic but it cannot be expected to act as such if used solely to lubricate the catheter; it should be injected first. The method of tying in a catheter is good and well illustrated, but are there no Foley catheters in New Zealand?

The subject-matter is well balanced and the teaching is good sound common sense; the illustrations are all to the point, the appendix of emergency operations is useful, and the references are kept within the bounds of what is appropriate. The book can be strongly recommended to all students and practitioners and will keep them abreast with modern developments in Urology.

Les Pancréatites Chroniques de l'Adulte. By H. SARLES and M. MERCADIER. 10¾ × 7½ in. Pp. 265, with 70 illustrations. 1960. Paris: L'Expansion Scientifique Française. 36 NF.

TRUE chronic pancreatitis is undoubtedly more common in France than in this country, so that a new French monograph is welcome. The main contributors are a physician and a surgeon with special interest in pancreatic disease, who have managed to present with clearness and honesty an unusual amount of morbid anatomical and radiological information.

An important distinction is made between the calcifying type of chronic pancreatitis and other forms of pancreatic fibrosis. The aetiology of the calcifying type is discussed in detail and histological evidence is produced to support the view that neither biliary reflux nor recurrent acute pancreatitis is a frequent aetiological factor. Although both alcoholism and a high fat intake predispose to calcifying pancreatitis, the earliest pancreatic lesions are characteristically focal, possibly due to obstruction of tributary ducts by mucinous material.

There are a number of interesting radiographs, including several operative pancreatograms illustrating gross changes in the ducts resulting from calcifying pancreatitis.

The chapter on the surgical treatment of chronic pancreatitis is extremely good. Considerable emphasis is placed upon operative pancreatography. Thus transduodenal sphincterotomy is advocated only when there is dilatation of the main pancreatic duct due to stenosis at the level of the sphincter, this being found in only 3 out of 45 patients with calcifying pancreatitis who were explored. Various direct procedures are discussed, and the author shows a preference for biliary or pancreatic drainage rather than ablation of diseased pancreatic tissue.

With the exception of some drawings in the surgical section, the illustrations are excellent, and there is a long bibliography. This is an up-to-date monograph which is one of the best now available to clinicians interested in chronic pancreatic disease.

First Aid in the Factory. By LORD TAYLOR, B.Sc., M.D., F.R.C.P., Medical Director, Harlow Industrial Health Centre. 8¾ × 6 in. Pp. 140, with 71 illustrations. 1960. London: Longmans, Green & Co. Ltd. 9s. 6d.

ANOTHER book on first aid when there has been such a spate of them during the last year! In spite of this fact this book will be found of real value to doctors and nurses who find themselves working in a factory or other large establishment. It is also a book for first-aiders themselves.

Lord Taylor has been assisted in the writing of this book by his colleagues at the Harlow Industrial Health Centre, Dr. W. N. Booth, Dr. B. S. Laing, and Dr. O. Ross.

Minor accidents and illnesses are common in factories, and accurate and suitable first-aid treatment can prevent incapacity. It should be remembered that in 1957 the people of Britain lost 275 million working days owing to certifiable industrial incapacity. Nearly half this loss was due to minor accidents and illnesses which could be properly treated at work—if the facilities were available.

This book is written in a simple but very practical style, with excellent illustrations showing the right and the wrong way of giving first-aid treatment.

We are particularly pleased to find that Lord Taylor still advocates the Holger Nielsen method of artificial respiration, and is not wedded to 'mouth-to-mouth' resuscitation, which is so difficult to teach—especially to schoolchildren.

Industrial first aid is an important problem to-day, and this book covers every aspect.

Modern Trends in Cardiology. Edited by A. MORGAN JONES, M.Sc., M.B., F.R.C.P. 9½ × 6½ in. Pp. 264 + ix. Illustrated. 1960. London: Butterworth & Co. (Publishers) Ltd. 70s.

THE "Modern Trends Series" of Butterworths have made their mark as most useful volumes on various branches of medicine and surgery.

The present volume is ably edited by Morgan Jones, and he is assisted by nineteen contributors who cover every aspect of cardiology.

During the last decade enormous advances have been made in this branch of medicine, and the treatment of atrial septal defects has now passed into the realm of Surgery.

There are sixteen chapters in this volume, and some of them are outstanding. The chapters on "Cardiac Muscle Metabolism", "Pulmonary Function in Heart Disease", and "Medical Aspects of Cardiac Surgery" are excellent.

A very comprehensive bibliography and references are to be found at the end of the book. This is an outstanding volume, and one which will be valued by all clinicians.

The Year Book of General Surgery 1960–61. Edited by MICHAEL E. DE BAKEY, B.S., M.D., M.S. 7¾ × 5 in. Pp. 616, with 184 illustrations. 1960. Chicago: The Year Book Publishers Inc. (London Interscience Publishers Ltd.) 60s.

THIS year book of general surgery gives a very good survey of the advances in Surgery which have taken place in the last year or so. The new techniques and operations are well described.

It is interesting to note that there is a tendency to reapply the Listerian doctrine of wound management as there is just as much wound sepsis as there was 20 years ago. A little judicious use of antiseptics would cut down wound sepsis a lot.

Chemotherapeutic agents for the treatment of malignant disease have increased of late, and phenylalanine, mustard, and thio-TEPA are used considerably in America.

This year book still provides a useful précis of surgical treatment as advocated in the literature during the last year.

Lectures on the Scientific Basis of Medicine (British Postgraduate Federation). With various contributors. Vol. 8. 1958–59. Edited by FRANCIS FRASER. 8½ × 5½ in. Pp. 467. Illustrated. 1960. London: Athlone Press. 45s.

THE eighth volume of *Lectures on the Scientific Basis of Medicine* contains twenty-four lectures, which cover a wide variety of subjects. These lectures should interest all clinicians, for they give an up-to-date review of modern medical research.

Dr. D. G. Evans gives a most interesting account of vaccination against poliomyelitis, while R. E. O. Williams deals in an admirable way with epidemic staphylococcal infection in hospitals. Professor E. F. Scowen contributes a masterly lecture on hyperoxaluria.

At the end of this volume there is a complete list of lectures which have been delivered since 1951.

Professor Francis Fraser deserves much praise from the profession for his foresight in initiating this series of lectures. This present volume will be the last he will edit, but no doubt his successor, Sir James Patterson Ross, will continue the series.

Instructional Course Lectures. Volume XVII, 1960. Edited by FRED C. REYNOLDS, M.D. 10$\frac{7}{16}$ × 8$\frac{5}{8}$ in. Pp. 420, with 358 illustrations. 1960. St. Louis: The C. V. Mosby Co. (London: Henry Kimpton.) 138s.

THIS large volume of lectures is divided into five parts, all of which are well illustrated with clinical photographs, radiographs, and charts.

Part I is devoted to fractures, and all the common fractures are discussed in a very practical manner. Part II deals with bone-graft surgery, while Part III is concerned with the orthopædics of childhood. Part IV covers miscellaneous subjects, such as disability evaluation and rehabilitation, and Part V is devoted to athletic injuries.

The whole vast subject of orthopædics is well covered in this volume, and the book will prove of real value to the younger generation of surgeons who are interested in this ever-growing branch of surgery.

The Operations for Inguinal Hernia. By MARK M. RAVITCH, M.D., and JAMES M. HITZROT, M.D. 10 × 6¼ in. Pp. 64, with 27 illustrations. 1960. St. Louis: The C. V. Mosby Co. (London: Henry Kimpton.) 30s.

THIS is a small monograph which deals with the operations performed on inguinal and femoral hernias by such pioneers as Bassini, Halsted, Wyllys Andrews, A. H. Ferguson, and Lotheissen. An historical account of each of these surgeons is presented, but nothing is said of the operations by Macewen, Coley, Kocha, and Bloodgood.

It is a great pity that this monograph is so restricted, and deals with relatively few of the great surgeons of the past who contributed so much to the surgery of hernia.

The Surgeon's Glove. By JUSTINE RANDERS-PETERSON, M.A. 9 × 5½ in. Pp. 95, with 12 illustrations. 1960. Springfield, Illinois: Charles C. Thomas. (Oxford: Blackwell Scientific Publications Ltd.) 36s.

THIS small monograph traces the history of the use of surgical gloves in the nineteenth century, and recalls the bitter arguments which took place between the antiseptic and aseptic surgeons. Controversies are described which took place in the great medical societies as well as heated exchanges of letters in the pages of leading medical journals.

It is interesting to read of the various forms of gloves which were invented for the surgeon's use—cotton, silk, leather, and rubber all had their advocates.

Atlas der gynakologischen Operationen. By O. KÄSER and A. IKLE. 8½ × 10¾ in. Pp. 451 + xii, with 707 illustrations. 1960. Stuttgart: Georg Thieme. DM.148.

THE attention of gynæcological surgeons is here drawn to a new 'Atlas' of gynæcological operations, which cannot be too highly commended. All current operations, if not each and every modification, are lucidly described and beautifully clearly illustrated. For those not yet set in their ways, alternative techniques are weighed up by reference to an international bibliography as wide as it is up to date, as well as by the authors' own experience. Those border-regions of abdominal surgery, proctology, and urology, which should be within the gynæcologist's capabilities, are fully considered.

An English edition of this work would certainly be very welcome.

Chirurgie du Rachis. By ANDRÉ SICARD. 9½ × 6½ in. Pp. 484 + iv, with 166 illustrations. 1959. Paris: Masson. Cloth bound, 7000 fr.

THIS book is one of a series inspired by Henri Mondor, who has encouraged leading French surgeons to contribute monographs on their various specialties. This volume, which is based on an extensive personal experience, is contributed by Professor Sicard, who is surgeon to the Hôpital Beaujon in Paris. It is an orthopædic work and is not primarily concerned with neurosurgical problems.

Over one hundred pages are devoted to the techniques of various operations on the spine. Among these percutaneous biopsy of the vertebral bodies is well described, and in view of the awakening interest in the use of posterolateral thoracotomy for treating lesions and malformations of the thoracic spine, it is satisfying to see a section devoted to this method. British surgeons have not neglected this approach; H. J. Richards, who has developed it over several years, demonstrated it at the Second Provincial Meeting of the Royal College of Surgeons of England in Cardiff in 1958, while A. R. Hodgson and F. E. Stock, in papers in this JOURNAL in 1956 and 1960, convincingly supported its use in tuberculosis. These authors are quoted, as well as J. Cauchoix and J. P. Binet of Paris, who also advocated this approach at a joint meeting of the Royal College of Surgeons of England with the Académie de Chirurgie de Paris in May, 1957 (*Ann. Roy. Coll. Surg. Engl.*, 1957, **21**, 237).

For the difficult task of exposing the bodies of the lower cervical and upper thoracic vertebral bodies the book follows Cauchoix and Binet in advocating a left cervical incision extended downwards into a median sternotomy with division of the left innominate vein. Most surgeons would probably prefer a high posterolateral thoracotomy, using an incision like that for thoracoplasty as advised by Hodgson and Stock, to this method.

The second section deals with injuries and traumatic paraplegia. The author has little enthusiasm for operative fixation, and the concept of compression and torsion injuries is not mentioned. The reader will look in vain for any reference to stable and unstable fractures.

The subjects of the painful spine, disk lesions, scoliosis, and congenital malformations are dealt with conventionally and a little disappointingly.

It is in dealing with tuberculosis, tumours, dystrophies, and less common diseases of the spine that the book finally comes into its own. For example, the problem of disk lesions in achondroplasiacs is mentioned, and there are good sections on hydatid disease of the spine and on vertebral angiomata.

The book is well produced, but references are not given for all authorities mentioned. The illustrations are good, but all the radiographs are printed as positives. The book is expensive even by modern standards, but will be useful as a work of reference.

Pathology of Tumours. By R. A. WILLIS, D.Sc., M.D., F.R.C.P., Consultant Pathologist to the Imperial Cancer Research Fund, London. Third edition. 9½ × 6½ in. Pp. 1002 + xvi, with 500 illustrations. 1960. London: Butterworth & Co. (Publishers) Ltd. 105s.

THIS third edition of Professor Willis's work will be most welcome, for it is the leading book on tumour pathology in the English language. There can be no doubt whatever that this new edition presents a complete and most lucid picture of tumour pathology in the light of present-day experience and research.

Much happens in the field of pathology in seven years, and Professor Willis has added some 800 additional references in this new edition.

This book will appeal not only to pathologists but to all clinicians who are interested in the subject of the pathology of tumours.

Rehabilitation of Hand Function. By A. N. LEONT'EV and A. V. ZAPOROZKETS. Translated from the Russian by BASIL HAIGH, M.A., M.B., B.Chir., and edited by W. RICHIE RUSSELL, C.B.E., M.D., D.Sc., F.R.C.P., Director, Department of Neurology, United Oxford Hospitals. Pp. 199 + xiii. 1960. Oxford and London: Pergamon Press. 60s.

THIS is a useful book, for it sets out the methods used in Russia for the rehabilitation of hand function following injury. There are some good illustrations, showing how tools can be modified for use by patients who have suffered injury and/or partial loss of the hand.

Perhaps one of the most interesting parts of this monograph are the various simple methods which are used in recording the disability of hand function.

This book has been produced by non-letterpress setting and photo-lithography. This has been done to save time and reduce the cost of production; notwithstanding this, the type is quite clear and easy to read.

This book will be widely read by all surgeons and physiotherapists who have the all-too-common injured hand to deal with.

Surgical Errors and Safeguards. By MAX THOREK, M.D., LL.D., Sc.D., F.I.C.S., F.B.C.S., F.P.C.S. (Hen.), D.C.M., F.R.S.M. Fifth edition. 10 × 6¾ in. Pp. 652 + xvi, with 455 illustrations. 1961. London: Pitman Medical Publishing Co. Ltd. £10.

IN the fifth edition of this large work Max Thorek has obtained the help of some twenty-three contributors, all well known in the various fields of modern surgery. The whole book has been entirely rewritten and its value enhanced. No surgeon to-day can be expected to be an expert in all the many and varied branches of the art and practice of surgery.

The various contributors have done their work well, and have set forth in an interesting way the surgical pitfalls which may arise during surgical operations. With such a team of experts, it is quite understandable that all safeguards that should be taken before, during, and after surgical intervention should be set out in detail.

This is an ideal book for the young surgeon, but its price is somewhat prohibitive.

The Urological Aspects of Bilharziasis in Rhodesia. By R. M. HONEY, M.D., F.R.C.S. (Edin.), Consulting Urologist, Salisbury Hospitals Group; and M. GELFAND, C.B.E., M.D., F.R.C.P., Consulting Physician, European and African Hospitals, Salisbury. 8½ × 5½ in. Pp. 71, with 38 illustrations. 1960. Edinburgh & London: E. & S. Livingstone Ltd. 7s. 6d.

A DISEASE which is seen only rarely in these islands is apt to escape recognition when it does appear. To-day, when air transport makes for rapid interchange between all parts of the world, it is of increasing importance for urologists and others to be aware of the possibility of bilharziasis and to know its effects on the urinary tract. As a result of a large experience of the disease in Rhodesia and Nyasaland Mr. Honey and Dr. Gelfand have given an authoritative account of the disease as it affects Europeans and Africans. The main differences in the racial manifestations are due to the more widespread infestation in the African owing to his delay in seeking treatment. Bilharzial carcinoma of the bladder occurred in none of 300 Europeans and in 4 of 100 Africans, but 80 per cent of the latter suffer from bilharziasis so the incidence of carcinoma might be coincidental. The most serious effects of the disease are to cause urinary obstruction, usually in the ureters, and modern surgical urological methods of treatment of such obstruction are applicable and often successful. Vesico-ureteric reflux may occur after relief of stenosis at the lower end of the ureter, but its effects are not important in the absence of increased intravesical pressure; patients with reflux have been followed for 20 years with no evidence of renal damage.

Perhaps it was considered beyond the scope of the book to include a detailed account of the medical treatment now given, but it would have added to its value. In its present form it gives a clear and concise account of the pathological effects of the disease, the methods of investigation, and the means of surgical correction.

Medullary Sponge Kidney. By TORE EKSTRÖM, BENGT ENGFELDT, CURT LAGERGREN, and NILS LINDVALL. 9½ × 6½ in. Pp. 73, with 28 pages of illustrations. 1960. Stockholm: Almquist and Wiksell. Sw.Kr.18.

ALTHOUGH a description of the changes in the kidney now detailed was given in 1908 by Beitzke, the condition of medullary sponge kidney was not recognized as a clinical entity until 1939, when the Italian radiologist Lenarduzzi gave a fuller account of it. Renewed interest has been aroused by the publication of sporadic cases and now culminates in this scholarly survey from Sweden which covers 44 patients, the largest single series yet recorded. It says much for the excellent records and methodical storage of the Karolinska Hospital that the authors were able to study radiographs going back to 1940, and even more for the excellence of the radiographic technique that they can now produce such superb reproductions of the excretion urographs.

The principal changes are the occurrence of cystic dilatations of the collecting tubules in the renal pyramids; these small cysts frequently contain stones. The condition was bilateral in more than half of the cases here reported, and its treatment is therefore difficult, being most often confined to the treatment of complications. The evidence presented supports the view that it is a congenital anomaly, possibly related to polycystic kidney. The diagnosis is more readily made by excretion urography than by retrograde pyelography.

The account is systematic, complete, and in every way excellent. It is from such work as this that further advances in our knowledge of renal pathology will spring. The book is small but is worthy of something better than a paper back.

Comparative Anatomy, Pathology and Roentgenology of the Breast. By HELEN INGLEBY, M.D., M.R.C.P., late Professor of Pathology, Women's Medical College of Pennsylvania; Research Pathologist on Diseases of the Breast, Albert Einstein Medical Center, Philadelphia, Pennsylvania; and JACOB GERSHON-COHEN, M.D., D.Sc. (Med.), Department of Radiology, Albert Einstein Medical Center; Assistant Professor of Radiology, Graduate School of Medicine, University of Pennsylvania. 8¾ × 5½ in. Pp. 472. Illustrated. 1961. Philadelphia: University of Pennsylvania Press (London: Oxford University Press). 80s.

IN many respects this is a unique book, for it presents a new and interesting light on the human breast and its pathology. It is the outcome of investigations which have been carried out over many years in the anatomy, pathology, and roentgenology of the breast.

It is interesting to read and see the normal histology of the human breast from the infant to the adult life. The cyclic changes in the breast are well described and illustrated, and the effect of pregnancy and lactation are set forth in a convincing manner. Congenital anomalies of the breast are well illustrated and the part played by roentgenology is beautifully portrayed.

The authors are quite correct in their opinion as to the advantages of serial sections through the entire breast in coming to a conclusion as to the complete pathology of the breast condition. They agree that any knowledge gained from the examination of whole sections needs to be supplemented by the tridimensional view that a radiograph can give. From the radiological point of view it is equally obvious that scientific roentgenography is possible only on the basis of a sound knowledge of the structures represented on the X-ray film.

The combination of the skill of the two research workers has resulted in a reclassification of diseases of the mammary gland. This deserves to be given a thorough trial in this country, for there can be no doubt that new and fertile ground has been discovered by Helen Ingleby and Gershon-Cohen.

A most stimulating and important book, which should be read by all surgeons and pathologists.

Techniques of Thoracotomy. By B. T. LE ROUX, M.B., Ch.B., F.R.C.S.E., Senior Registrar, Regional Thoracic Unit, Edinburgh. 9¾ × 7¼ in. Pp. 94, with 65 illustrations. 1961. Edinburgh: E. & S. Livingstone Ltd. 55s.

THIS is a beautifully illustrated monograph depicting the operative procedures involved in the operations of thoracotomy. Many of the operations are shown in colour and are well reproduced. Sir Clement Price Thomas, who writes a foreword to this book, has nothing but praise for it, and we heartily endorse his sentiments.

An outstanding production, well illustrated and produced, and yet the price is most moderate.

Neurovascular Compression Syndromes of the Shoulder Girdle. By LOUIS M. ROSATI, M.D., and JENE W. LORD, M.D. 9×5½ in. Pp. 168+vi. Illustrated. 1961. New York and London: Grune & Stratton, Inc. $7.25.

THIS volume of the series of modern surgical monographs edited by I. S. Ravdin and R. H. Orr and written by two professors of clinical surgery in the Postgraduate Medical School of New York, who are also attending surgeons at the Bellevue and University Hospitals, is a clearly written, well-illustrated, and well-documented account of the subject. There is a foreword by Irving S. Wright, to whom, along with J. W. Hinton and the late Dan Elkin, the book is dedicated. The anatomy, pathogenesis, diagnosis, and treatment of the various syndromes producing pain, weakness, or vascular insufficiency in the upper limb are considered. The book concludes with a summary of the case histories of 51 patients with neurovascular compression syndromes at the shoulder girdle who have been under the care of the two authors. The authors' claim to make the book a compact, practical guide to the understanding and treatment of such syndromes is well borne out and there is little to criticize in the account of the way in which the neurovascular outflow to and from the arm may be involved by abnormal structures. The illustrations are excellent and consist of plates, reproductions of X-ray films, and line drawings, but in certain of them the lowest trunk of the brachial plexus is unfortunately referred to as the lower cord. In the differential diagnosis of pain in the arm, there is only scarce mention of carpal tunnel compression, which is listed under peripheral entrapment neuropathy [*sic*], but American authors still appear to be slow to recognize this syndrome. In contradistinction to some American monographs, in the list of 99 references quoted in the text many are from British sources. The authors advocate resection of the clavicle in cases of costo-clavicular compression, commenting on its relative simplicity as compared with resection of the underlying rib. They quote Gurd (1947) that the clavicle is "one of the readily spared bones of the skeletal system", a fact to which G. Grey Turner many years ago first drew attention and which he frequently emphasized.

Neurologists as well as surgeons may profitably study this account of these syndromes, particularly since many of the former in this country to-day are perhaps unjustifiably sceptical of the existence of certain of them.

Orthopaedics. By GEORGE PERKINS, M.Ch., F.R.C.S., Consulting Orthopædic Surgeon, St. Thomas's Hospital, London. Consulting Surgeon, Rowley Bristow Hospital, Pyrford. 9¼×6 in. Pp. 975, with 577 illustrations. 1961. London: The Athlone Press. 126s.

ALTHOUGH there are many books and works on orthopædics, there is always room for another if it adds to our surgical knowledge and experience. George Perkins has certainly written a stimulating book quite out of the ordinary run of surgical books, and this is because it relates his experiences in orthopædic practice over the years. He has no axe to grind and he is forthright and dogmatic in his statements. We like to see such conviction and candour in any medical book.

Another factor which makes this an outstanding book is the excellence of the illustrations, which are very numerous. Any book on orthopædics cannot be of real value if the radiographs are not of good quality: in this book Perkins has picked out just those illustrations which make the text appear simple yet interesting. Some of the line illustrations are quite original and this in itself is another good point. New facets on teaching and expression are always encouraging, there is far too much sameness in the modern text-books.

This book, in our opinion, is just what is needed to-day.

BOOK NOTICES

[*The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to our readers.*]

The Perception of Muscular Work: A Psychophysical Study of Short-time Work on the Bicycle Ergometer. By GUNNAR BORG and HANS DAHLSTROM. 9¼×6 in. Pp. 26. Illustrated. 1961. Sweden: The Umea Research Library.

The Surgical Treatment of Portal Hypertension, Bleeding Esophageal Varices and Ascites. By M. JUDSON MACKBY, M.D., D.A.B.S., F.I.C.S. 10×6½ in. Pp. 250+xviii. Illustrated. 1961. Springfield, Illinois: Charles C. Thomas. (Oxford: Blackwell Scientific Publications Ltd.) 84s.

Procedures in Vascular Surgery. By RICHARD WARREN, M.D., Clinical Professor of Surgery, Harvard Medical School. 10½×8 in. Pp. 211+x, fully illustrated. 1960. London: J. & A. Churchill Ltd. 85s.

Parkinsonism, its Medical and Surgical Therapy. By IRVING S. COOPER, M.D., Ph.D., F.A.C.S. 11×8¾ in. Pp. 239+xii, with 111 illustrations. 1961. Springfield, Illinois: Charles C. Thomas. (Oxford: Blackwell Scientific Publications Ltd.) £6 12s.

The Transplantation of Tissues and Organs. By MICHAEL F. A. WOODRUFF, M.D., M.S. (Melb.), F.R.C.S., F.R.C.S.E., F.R.A.C.S. 9¾×6¼ in. Pp. 777+xxxiv, with 196 illustrations. 1961. Springfield, Illinois: Charles C. Thomas. (Oxford: Blackwell Scientific Publications Ltd.) £10 4s.

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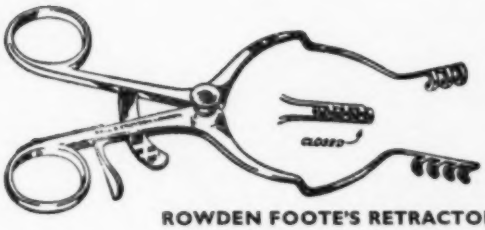

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